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In any endocrinal disease

Def:- Hyper / Hypo of ----- hormone + ----- age

Aetiology:-

Hyper	Hypo (4Ts)
- Hyperplasia - Adenoma - Iatrogenic - Para-malignant - + -----	- Trauma (Direct - haemorrhagic) - Tumors (1ry - 2ry) - TB (Granuloma) - TTT (surgical) - + -----

C/P:- Hyper or Hypo

Investigation:-

1- Hormonal assessment

Static	dynamic
Serum level without any alternation (as fasting ----)	To check the changes after:- Stimulatory test:- for Hypo Inhibitory test:- :- for Hypo

2- hormonal effect

(eg metabolic products)

3- Images (usually for cause detection)

TTT:-

Hyper	Hypo (4Ts)
- Symptomatic - Surgical - Antagonist (+)	- Symptomatic - Replacement



(maestro of endocrinal glands)

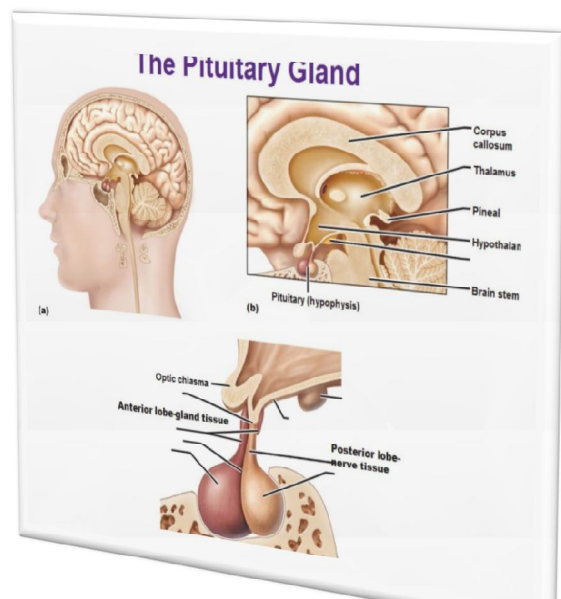
Anatomy:- 2 lobes separated by a pituitary cleft

1.Site:

- Inside the sella tursica
- Covered by diaphragm sellae
- Connected to hypothalamus by portal circulation and pituitary stalk

2.Relations:

- Anterior: optic nerve
- Posterior: post clenoid process, dorsum sellae, brain stem
- Superior: optic chiasma, hypothalamus, and 3rd ventricle.
- Lateral : cavernous sinus & temporal lobes
- Inferior: sphenoid air sinus



3. Blood supply:

- Arterial: superior & inferior hypophyseal artery (from ICA)
- Venous: hypothalamo-hypophyseal portal circulation.

4. Embryology:

- Anterior lobe: develops from Rathke's pouch, a diverticulum of the roof of primitive buccal wall.
- Posterior lobe: developed from floor of diencephalons.

Remnant of Rathke's pouch can turn malignant named "craniopharyngioma" or suprasellar tumor"

Hypothalamic – Hypophyseal Control:

The hormones of hypothalamus reach anterior pituitary through the **hypothalamo-hypophyseal portal circulation**. These hormones are:

a) Release factors (RF):

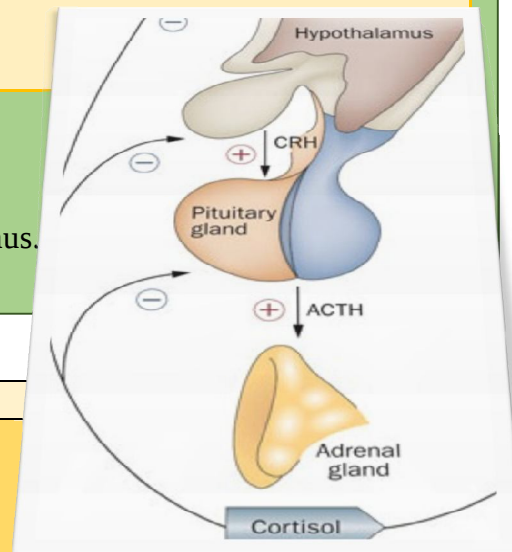
1. Thyrotropine releasing hormone (TRH)
2. Growth hormone releasing factor (GH-RF)
3. ACTH-RF
4. Prolactin- RF
5. Gonadotrophin releasing factor (LH & FSH-RF)
6. Melanocyte stimulating hormone – RF (MSH-RF)

b) Release – inhibiting factor (RIF):

1. GH-RIF=somatostatin
2. Prolactin-RIF = dopamine
3. MSH – RIF

The control of these factors is regulated by:

- CNS control: Stress, emotion
- Negative feedback:
 - Long feedback : from target organ to hypothalamus.
 - Short feedback: From pituitary to hypothalamus

**Structure & Functions of pituitary Gland:****Anterior Pituitary****Acidophil cells:-**

- Growth hormone (GH)
- Prolactin hormone

Basophils:-

- Gonadotrophin (FSH - LH)
- TSH
- ACTH
- MSH (not in humans)
- B-lipotropin (pigmenting hormone in humans)

Chromophobe cells:- unknown function

Posterior pituitary

- **ADH:-** from the supraoptic nucleus in the hypothalamus.
- **Oxytocin:-** from the paraventricular nucleus in the hypothalamus.

FSH: stimulates graffian follicles in ♀ and spermatogenesis in ♂

LH : stimulates ovulation in ♀ and secretion of testosterone in ♂

Diseases of hypothamic-pituitary axis

	Hyper-function	Hypo-function
GH	Gigantism Acromegaly	Pituitary dwarfism Pan-hypopituitarism (Simmond-Sheehan)
Prolactin	Hyper-prolactinaemia	
TSH		Hypothyroidism (2ry)
ACTH	Cushing's disease	
Post.	SIADH	Diabetes insipidus (DI)

Growth hormone:- Polypeptide hormone activates liver & other tissues to secrete Insulin-like growth factor- 1 (IGF – 1) previously named somatomedin C.

Action: Mainly **Metabolic action**

- Carbohydrate: **Diabetogenic** ($\uparrow$ gluconeogenesis & $\downarrow$ uptake of glucose (anti-insulin)).
- Fat: **lipolysis:-** leading to $\uparrow$ free fatty acids.
- Protein: **anabolic** $\uparrow$ chondrogenesis, osteogenesis, growth of muscles and viscera.
- Electrolytes: **Salt and water retention** ($\uparrow$ Na (Aldosterone like)- $\uparrow$ Ca ($\uparrow$ intestinal absorption) - $\uparrow$ K & PO₄ (2ry to $\uparrow$ protein synthesis)

N.B. It's similar structurally to prolactin & human placental somatomamotropin factors affecting GH (regulations)

Stimulatory	Inhibitory
- Hypoglycaemia (Insulin stimulatory test) - Amino acids (arginin stimulatory test) - Stress, exercise (hypothalamic effect) Central action - Estrogen, α - receptors, dopamine, GABA, Serotonin	- Glucose

Acromegaly

Definition: increased GH secretion after fusion of epiphysis (after puppetry)

Aetiology:

1. Acidophil adenoma (or hyperplasia)
2. Hypothalamic disorder:- ++ GHRF or – GH-RIF

Clinical Picture: (Metabolic + Others:- neurological and pressure)

A- Metabolic action:

- a) **CHO:** **DM** in 30% of cases (relatively insulin resistant)
- b) **Fat:** excess **lipolysis** with loss of SC fat & wrinkling of skin in forehead and face with excess grease sweating (sign of activity).
- c) **Protein:** excess **growth** of bones, muscles & viscera:

- Bone:

1. **Acromegalic facies "Ape like"**

- Big skull, prominent frontal sinuses, supraorbital ridges, malar bones & mastoids.
- Enlarged nose, ears, lips & tongue (macroglossia, with sleep apnea)
- Prognathism (prominent lower jaw) with separated teeth
- Hypertrophy of larynx with husky voice.

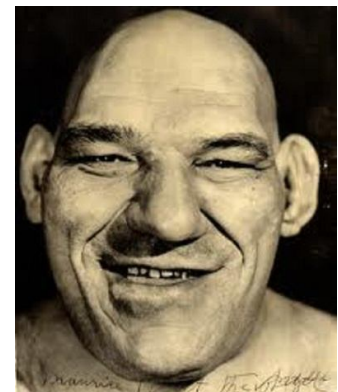
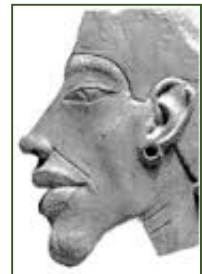
2. **Feet & hands "spade like"** enlarged with blunting of tips with Frequent change of rings & shoes.

3. **Kyphosis**

4. **Osteoarthritis:** with swollen joints & thick synovial membrane

- Viscera:- Hepatosplenomegaly, cardiomegaly (+ HF due to hypertension & cardiomyopathy) and enlargement of thyroid gland.

- Muscle: Early $\uparrow$ in power, later on decrease with muscle wasting (decline stage)



- d) **Electrolytes:** **Na retention** leads to hypertension (+ hypertrophy of wall of BVs)
- e) **Prolactin:** damage of pituitary stalk or presence of mixed GH & prolactin secreting tumor):
- In males gynecomastia & galactorrhea
 - In females amenorrhea or menstrual disturbances
 - Hypogonadism (prolactin inhibits gonadotrophins)

Others:**Neurological manifestations:**

- a) Emotional lability:- depression
- b) Peripheral neuritis (parasthesia of hands & feet): **due to**
- Interstitial neuropathy
 - Carpal & Tarsal syndromes
 - Diabetic neuropathy.

Causes of death:

1. Sleep apnea (respiratory)
2. Cardiovascular (HF)
3. DM
4. Colonic polyps or cancer

Pressure manifestations: in case of large adenoma which might lead to visual defects (bitemporal hemianopia)

Investigations:

- 1- Hormonal assessment
- 2- Hormonal effect
- 3- Images

1- Hormonal assessment

- **Static** - **GH level:** increased (N=1-5 ng/ml in adult – 20 ng/ml in children)
- **Dynamic** - **IV glucose** fails to decrease GH level
- **Insulin-like growth factor-1 (IGF-I):** ↑level (more reliable than GH)
- **Hyper-prolactinemia in 1/3 of cases**

2- Hormonal effect

- Increase glucose & FFA, hypercalcemia & hyperphosphatemia

3- Images:- causes + effect

For cause:- X-ray, CT, MRI skull for tumor (wide or ruptured sella tursica)

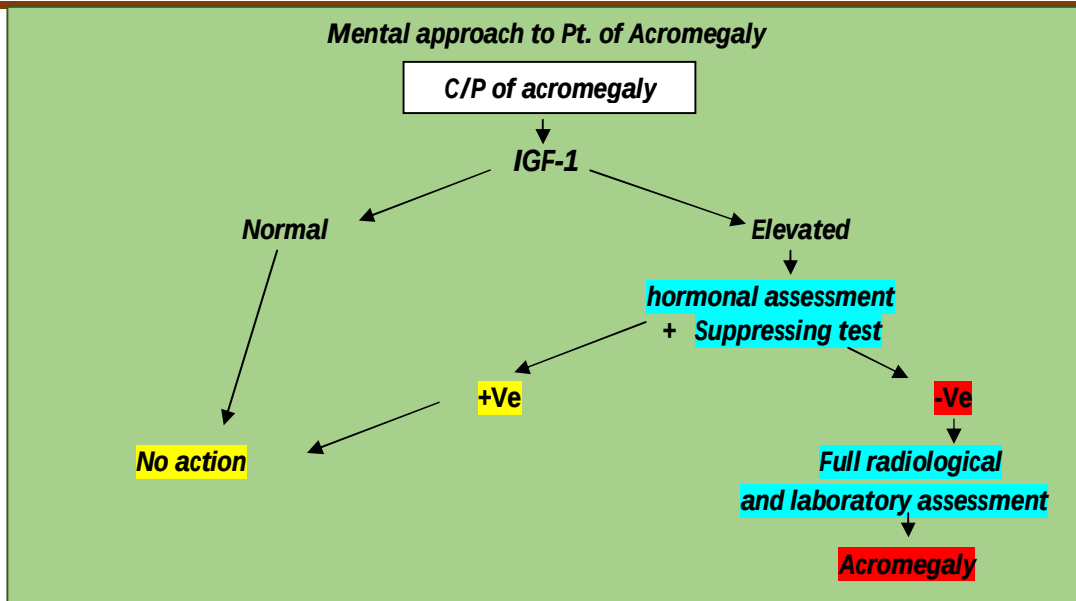
Effect:-

X-ray:**1. Skull:**

- Thickening of cortex
- Pneumatization of frontal air sinuses
- Prominent external occipital protuberance
- Big mastoid process
- Prognathism and wide separation of teeth
- wide or ruptured sella tursica

2. Hands: Periosteal thickening of phalanges + tufting of terminal phalanges "mushroom shape or arrow head"**3. Spine:** ↑anteroposterior diameter of vertebrae, kyphosis & osteoporosis

Measurement of **thickness of skin fold** over dorsum of hands & lower part of triceps (>3.5 mm at 25 y. or > 3 mm at 65 y. suggests acromegaly).

**Treatment:**

1. Symptomatic treatment: of DM, hypertension & hypogonadism
2. Irradiation of pituitary (proton or by implantation of radio-gold or yttrium 90)
3. Surgical: hypophysectomy (transphenoidal) in **resistant** cases
4. Medical hypophysectomy (hormone antagonist):
 - a) Dopamine agonist:
 - **Bromocriptin** (parlodel) which--GHRF in hypothalamus (1.25 mg at bed time & ↑ gradually to 15 mg/d)
 - Cabergoline: drug of choice – as Bromocriptin but few side effects
 - b) Somatostatin analogue (GHRIF): **Octreotide** 25-50 ug/ 12 hrs SQ
 - c) Growth hormone receptor antagonists:- Pegvisomant daily SQ (**Somavert**)

recent

Gigantism

Definition: Increased GH secretion before fusion of epiphysis (**before puberty**)

Aetiology:

- Hyperplasia of acidophil cells
- Acidophil adenoma

Clinical picture:

1. Generalized overgrowth of metaphysis of long bones leading to **disproportionate gigantism** (span > height + lower segment > upper segment)
2. Later on features of acromegaly develops
3. End stage or decline stage:- weakness, fatigue due to pituitary insufficiency

DD Tall stature

Definition: height above 97th percentile of normal people of the same age & sex.

	Built	Others
Familial & racial The commonest	proportionate	normal GH level
Gigantism	disproportionate	High GH level
Hypogonadism "Ennuch"	disproportionate	+ hypogonadism (feminine)
Cerebral gigantism Soto's syndrome	in the 1 st 5 years of life only	+ MR + Big skull - normal GH level
Marfan's syndrome	See later	
Klinefelter (xxy)	Tall, slim and underweight	
Homocystinuria	MR + coloured lens + thrombosis + homocystin in urine	
Hyperthyroidism	Early accelerated growth – later on shorter stature	
Sexual precocity		

DD of dwarfism

Definition : height below the 3rd percentile of normal people of the same sex & age

Aetiology:

A- Familial; the commonest

B- Genetic disorder:

1. Mongolism (Down syndrome): Trisomy 21
2. Turner's syndrome (XO): ovarian dysgenesis, 1ry amenorrhea, webbing of neck, increase carrying angle, coarctation of aorta
3. Microcephaly:
4. Progeria: premature senility.

C- Endocrinal causes:

1. **GH:** Levi-Lorain, Frohlich's & Laurence-Moon-Biedle syndromes.
2. **T4:** cretinism & juvenile myxedema.
3. **Sex hormones:** precocious puberty (tall child short adult).
4. **Cortisol:** Cushing syndrome or excess steroid treatment (cortisol block the ability of GH to produce somatomedin).
5. **Insulin:** Juvenile DM- excess glucose GH

D- Skeletal causes:

A- Congenital	B- Acquired
1. <u>Achondroplasia:</u> short limbs & normal trunk	1. Rickets
2. <u>Osteochondrodystrophy:</u> limbs & trunk are short and deformed	2. Paget's disease
3. <u>Osteogenesis imperfect:</u> fragile bone, pathological fracture + malfusion & dwarfism, joint dislocation, blue sclera, deafness due to otosclerosis	3. Pott's disease

E- Chronic severe illness during childhood:

1. **CVS:** rheumatic fever, congenital heart disease
2. **Lung:** polycystic lung
3. **GIT:** malabsorption, lipid storage, parasitic infestation, malnutrition, liver cirrhosis
4. **Kidney:** chronic nephritis.

GH deficiency**Pituitary Dwarfism**

Levi-Lorain syndrome 1ry deficiency of GH	Froehlich's syndrome	Laurence-Moon-Bidel
1- Pituitary :- idiopathic, cyst or craniopharyngioma 2- End organ unresponsiveness (African pigmies)	- Idiopathic - hypothalamo-pituitary tumor (craniopharyngioma)	Froehlich's + poly/syn-dactyly + skull deformity + MR + retinitis pigmentosa.
1. Proportionate dwarfism 2. Childish features 3. Hypogonadism	Levi-Lorain + Post. Pituitary : DI (polyurea - polydepsia) Hypothalamus : Polyphagia, hypersomnia. Samboxa shape obesity + MR.	
Treatment:- - Human GH 20-45 mg / monthly – Now replaced by recombinant GH - Thyroxin with gonadal hormone - Gonadotrophin (for cryptorchidism):- before age of 9 years to prevent testicular atrophy.		

Dwarfism + hypogonadism = Infantilism

Prolactin Hormone

Physiology:- production of milk

- Growth of ducts & alveoli of estrogen and progesterone prepared female breast
- During Pregnancy:- Maintains corpus Luteum till placental formation.
- GH like action

factors affecting Prolactin (regulations)

Stimulatory	Inhibitory
Ss:- Stress - Sleep - Suckling - Serotonin TRH -Opiates -VIP	- Dopamine - Methsyrgide - Naloxone

Hyperprolactinemia**Aetiology:-**

1. **Physiologic causes**: pregnancy, lactation, stress, sleep.

2. Drugs:

- Dopamine antagonists: phenothiazine, metoclopramide.
- Dopamine depletion: methyl-dopa, reserpine
- Others: Estrogen -Opiates

3. Diseases:-

- Pituitary tumors: acidophil adenoma causing Acromegaly & gynecomastia
- Hypothalamus diseases (inhibits dopamine): granulomas, sarcoidosis.
- Primary hypothyroidism : ↑TRH
- Liver cirrhosis (decreased metabolism)
- CRF (decreased clearance).

Prolactinoma:-

- microprolactinoma:- < 10 mm
- macroprolactinoma >10 mm.

Clinical picture:**Hormone action:**

1. In males: impotence, infertility, gynecomastia & galactorrhea
2. In females: galactorrhea-amenorrhea (suppress **GnRH**), infertility & osteoporosis (estrogen deficiency)

Pressure manifestations: in case of large adenoma which might lead to Panhypopituitarism

Investigations:

1- Hormonal assessment:- Serum prolactin: > 300 ng /ml is diagnostic of pituitary adenoma (normally < 15 ng/ml in males and < 20 ng/ml in females)

2- Hormonal effect:- Thyroid functions for myxedema

3- Images:- CT & MRI brain but useless in microadenoma < 10 mm

Treatment:

1. Surgical removal: transphenoidal or transcranial in large tumor with pressure symptoms or failed medical treatment.
2. Radiation by proton or alpha particles
3. Prolactin antagonist: (Dopamine agonist)
 - **Bromocriptin (parlodel)** 10-15 mg/day. Resumption of fertility and shrinkage of small tumors usually occurs
 - **Cabergoline:** 250-1000 ug/week, fewer side effects.
 - **Quinagolide:** 50-150 ug/day
4. Treatment of cause: e.g. myxedema

Panhypopituitarism

Sheehan syndrome – simmond's disease

Aetiology: (Sheehan + Ts + others)

1. **Sheehan syndrome** "pituitary apoplexy" : pituitary infarction following severe postpartum hemorrhage (vascular spasm & circulation shift to post. pituitary)

2. **Ts**

- TTT:- Hypophysectomy or pituitary irradiation
- Tumor:- chromophobe adenoma, supra sellar, end stage of acidophil adenoma
- Traumatic: fracture base of skull
- TB: Granulomas: TB, gumma, sarcoidosis, Histiocytosis, (Hand Schuller Christian disease)

3. **Others:-**

Idiopathic : autoimmune

Congenital:

- Kallmann's syndrome (isolated deficiency in gonadotrophins)
- Empty sella syndrome

4T

Clinical Features: (Hormonal effect + Pressure manifestations + Hypothalamic S)

The initial features are usually vague. GH is the initial hormone to decline then gonadotrophins, TSH and ACTH

Hormonal effect:

1. **↓Prolactin** : failure to establish lactation after delivery (**1st presentation**)
2. **↓FSH/LH** : amenorrhea, impotence, loss of libido, atrophy of breast & genitalia, loss of pubic and axillary hair (but no hot flushes)
3. **Thyroid deficiency** –↓ TSH
 - a) Myxedema
 - b) Hypothermic coma may occur on exposure to cold
4. **Adrenocortical insufficiency:** ↓ACTH

Hypoglycemia, infection:

- Hypopituitary crisis: on exposure to stress
- Present with acute abdomen like picture

2 differences from Addison disease:

- 1- **No pigmentation** " absent ACTH" + pallor & depigmented area (absent MSH & anemia)
- 2- No marked **hypotension**: presence of aldosterone

5. **Deficiency of GH:** (no obvious C/P in adults) skin wrinkling, weakness, wasting.
6. **Coma:-** occurs terminally due to hypoglycemia, hypothermia or tumor pressure on RF.

Pressure manifestations: headache bitemporal hemianopia

Hypothalamic syndrome:- as above + DI

Investigations:**1- Hormonal assessment**

- 1- Hormonal assessment
- 2- Hormonal effect
- 3- Images

Static	dynamic
a) FSH & LH + sex hormones : low b) TSH + T3 & T4 : low c) ACTH + corticosteroids: low	<u>Combined insulin tolerance test:-</u> • Determine fasting blood sugar, then IV insulin is given then TRH & GH-RH. Estimate every 1/2 hour blood sugar, GH, TSH, FSH, LH, prolactin & cortisol. • Normally:- blood sugar should fall to 40% & level of all hormones should increase 3 folds. • Failure to do so indicates hypopituitarism.

2- hormonal effect:- Hypoglycemia, normochronic anemia

3- Images (usually for cause detection)

1. X-ray sella tursica

- a. Intracellular tumor
 - Ballooning of sella
 - Double floor in eccentric tumor
 - Destruction of dorsum sellae & posterior clinoid ± encroachment on sphenoid
- b. Suprasellar tumor: saucerisation of sella & calcification

2. **CT scan & MRI** : the best – in Sheehan syndrome, sella tursica is normal

Differential Diagnosis:

1. **Primary hypogonadism**: hypogonadism, gigantism, high FSH / LH
2. **Adrenal hypocorticism**: skin pigmentation, high ACTH, marked hypotension
3. **Anorexia nervosa**: normal hair & breasts, aggressive attitude, normal cortisol, high GH (from hypoglycemia).
4. **Pernicious anemia**: see blood picture & serum B 12
5. **Thyroid myxoedema**

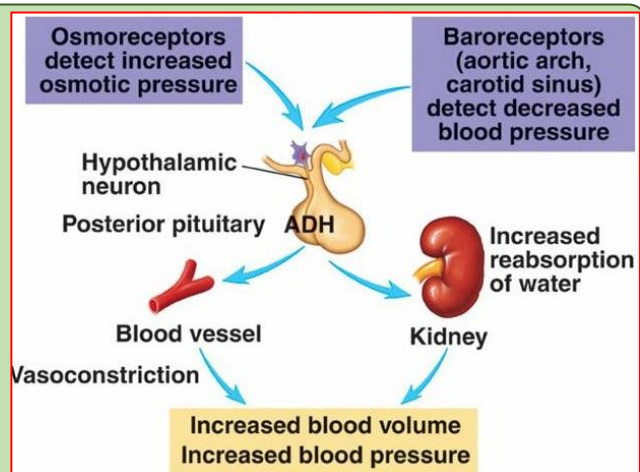
Treatment:

- I- For **coma**: glucose and saline infusion + avoid cold weather or stress.
- II- **Hormone replacement**:
 1. **Hydrocortisone**: 25-75 mg/day (**before thyroxin**)
 2. **Thyroxin**: should follow cortisol with a gradual increasing dose (0.1 mg – 0.2 mg to avoid adrenal failure)
 3. **Gonadal** hormones:
 - In males: methyl testosterone 25-50 mg /day
 - In females: oestradiol 0.02 mg/day for the first 21 days of each month.
 - **GnRH for treatment of infertility**.
 4. **Recently**: purified pituitary hormone or hypothalamic RH
- III- Treatment of **cause**: e.g. removal of chromophobe adenoma

Posterior pituitary hormones**Anti diuretic hormone (ADH)**

Physiology:- synthesized in hypothalamus & pass down the neural axon to be stored in post pituitary (**neurosecretion**).

- Stimulate water reabsorption by renal collecting tubules - higher doses cause VC.

**Factors affecting ADH (regulations)**

Stimulatory	Inhibitory
Osmoreceptors :- hyperosmolarity - hypovolemia	hypertension
Central :- pain, stress, nicotine and carbamazepin	cold weather

Diabetes insipidus "Tasteless Diabetes"

Definition: Impaired water reabsorption by kidneys due to decrease ADH secretion by post. Pituitary or impaired response of kidneys to ADH

Aetiology:

I- **Familial DI**– Walfram syndrome: Hereditary DI, due to defects in osmoreceptors
(**DIDMOAD**: DI, DM, Optic Atrophy & Deafness)

II- Damage of **hypothalamo-hypophyseal axis** "Central DI" (**Neurogenic**):

- a. Idiopathic
- b. Tumors (intra or suprasellar)
- c. Trauma: head injuries, after hypophysectomy
- d. Granulomas: TB, sarcoidosis
- e. ttt:- after hypophysectomy

III- **Nephrogenic DI**:

- a. Hereditary: X-linked disease, with renal tubules are insensitive to ADH.
- b. Acquired diseases:
 - Renal tubular acidosis
 - Sick cell anemia
 - Hypokalemia
 - Hypercalcemia
 - Drugs: lithium, methoxyfluorane, and democlocycline

Clinical Features:

Hormonal effect:

1. **Polyurea** (>50 ml/Kg/day) & nocturia.
2. **Polydipsia**- dehydration, weight loss, low grade fever, shock & encephalopathy may occur
3. **Hypovitaminosis**: loss of water-soluble vitamins in urine

Features of cause e.g. pituitary tumors

DI features may be hidden by associated cortisol deficiency in panhypopituitarism.

Investigations:

1- Hormonal assessment

Static :- ADH:- decreased

Dynamic (stimulatory - leveling)

Test hypothalamus "nicotine test":- (1-3 mg)

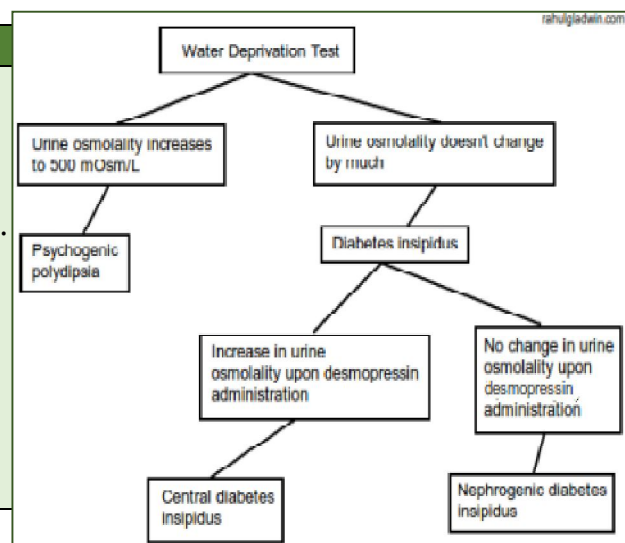
- Stimulates hypothalamus = ADH = oliguria.
- –ve in hypothalamo hypophyseal axis lesion.

Test osmoreceptors: Hypertonic NaCl IV

- Stimulates osmoreceptors = oliguria.
- –ve in familial type.

Test kidney "pitressin test":

- IM pitressin = causes oliguria.
- –ve in nephrogenic DI.



2- hormonal effect:-**1. Urine :**

Polyurea - no pathological constituents - low urine osmolarity

Urine osmolarity doesn't increase after 8 hrs water deprivation

2. Serum: increased osmolarity and serum Na level**3- Images** (Skull X-ray, CT scan & MRI: exclude tumors)**Differential Diagnosis:**

From other causes of Polyurea (urine volume > 1500 cc/day)→ look nephrology.

Treatment:**1- Symptomatic treatment:**

- Diet:**
- a- Excess fluids & vitamins with reduction of salts intake
 - b- Avoid purines (coffee, tea)

2- Replacement therapy:-

- a) **Pitressin** tannate in oil : 3-5 Units –IM every other day
Side effects: pallor, angina, colic, bronchospasm, and uterine contraction
- b) Des-amino arginine vasopressin (DDAVP):
Minirine or desmopressine – Intranasal 10-20 ug /12-24 h.
It has very low side effect compared to pitressin
- c) **Drugs sensitize renal tubules** to endogenous ADH:
 - a. **Chlorpropamide:** (side effect:- hypoglycemia).
 - b. **Carbamazepine** (Tegretol)
 - c. **Thiazides** diuretic: effective in nephrogenic DI (paradoxical effect)

Thiazide or indomethacin can be used to create mild hypovolemia which encourages salt and water uptake in proximal tubule and thus improve nephrogenic diabetes insipidus.

Syndrome of inappropriate ADH secretion (SIADH)

Causes:

1. Tumors: of lung (Small cell), prostate, thymus, pancreas & lymphomas.
2. Pulmonary: pneumonia, TB, lung abscess
3. CNS: meningitis, tumors, head injuries, subdural & cerebral abscess and SLE vasculitis.
4. Metabolic: alcohol withdrawal – porphyria
5. Drugs: chlorpropamide, carbamazepine, cyclophosphamide

Clinical Picture:

1. Water retention results in **dilutional hyponatraemia** manifested with nausea, confusion, irritability and later on convulsions and coma (3Cs).
2. There is no edema or hypertension

Investigations:

- 1- **Hormonal assessment**:- increased ADH level
- 2- **Images** (For detection of the cause)
- 3- **hormonal effect**:-
 1. **Urine** : high osmolarity – high sodium >30 mmol/L
 2. **Serum**: Decreased osmolarity and serum Na level
+ Normal renal, adrenal and thyroid functions.

Treatment:

1- Symptomatic treatment:

Diet: a- Restriction of fluid intake to 500-1000 ml/day

2- Hormone antagonism: **Democlocycline**: inhibit action of ADH on renal tubule in severe resistant cases– SE: photosensitivity.

3- For severe hyponatraemia: **hypertonic saline (1.8%)** is given slowly
IV + frusemide to avoid fluid overload

4- Treatment of cause:

Pituitary tumors

Pituitary tumors: 2 types

1. Intracellular: acidophil, basophil, chromophobe adenoma
2. Suprasellar: craniopharyngioma "remnant of Rathke's pouch"
(look neurology for details)

Clinical pictures:-

A- Haedach (triphasic):-

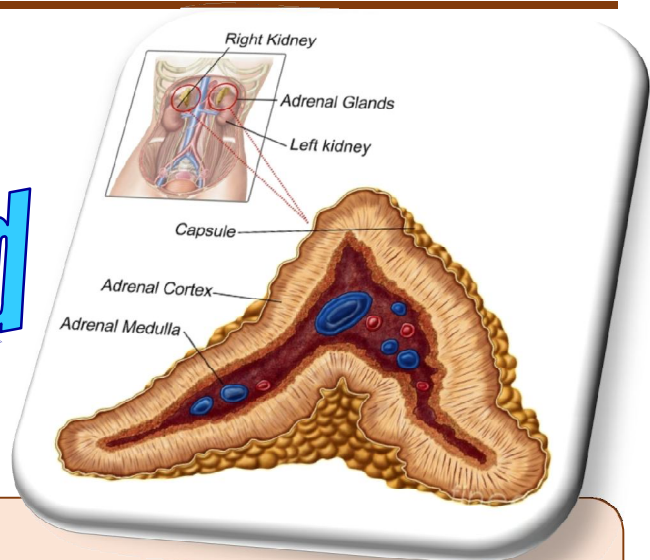
- 1- bitemporal caused by increased intrasellar pressure
- 2- Relieved after ruptured diaphragma sellae
- 3- Occipital caused by increased intracranial pressure

B- Pressure manifestation:- (look neurology for details)

C- Endocrinal manifestations:- according to the affected cells

2

Supra-renal gland

**Anatomy:-**

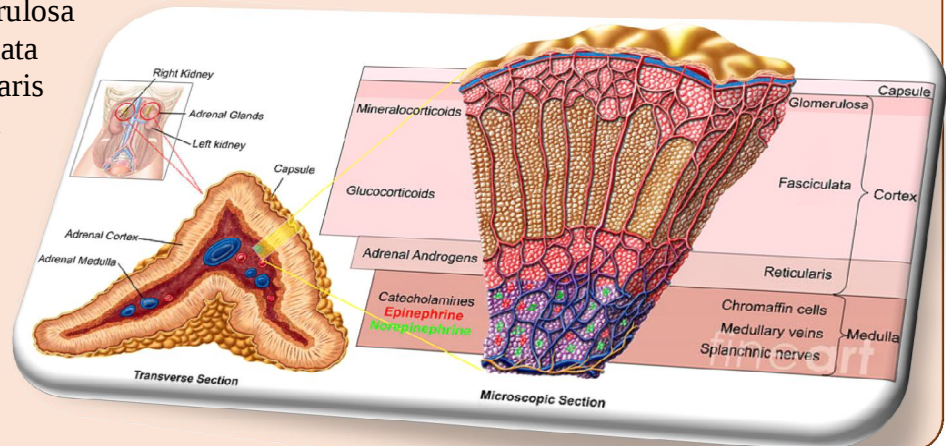
- Two glands, yellowish- brown in colour
- Each is related to the medial part of the upper pole of the kidney
- On the crus of diaphragm opposite the vertebral ends of 11th inter-space and the 12th rib.

Arterial supply	Venous drainage
1. Superior suprarenal artery (from phrenic artery)	1. Rt. Suprarenal vein to IVC
2. Middle suprarenal artery (from aorta)	2. Lt. suprarenal vein to left renal vein
3. Inferior suprarenal artery (from renal artery)	

Histology:

Each gland is divided into:

1. Adrenal cortex which includes 3 zones:
 - ★ Zona glomerulosa
 - ★ Zona fasciculata
 - ★ Zona reticularis
2. Adrenal medulla

**Diseases of suprarenal gland:**

	Hyper-function	Hypo-function
adrenal cortex	Conn's syndrome : ↑aldosterone. Cushing syndrome : ↑Cortisol. Adrenogenital hyperplasia : ↑androgen.	Addison's disease
adrenal medulla	Pheochromocytoma	

A- Hyper-function of Adrenal Cortex

Hyperfunction of zona glomerulosa Conn's syndrome (Primary hyperaldosteronism)

Aldosterone

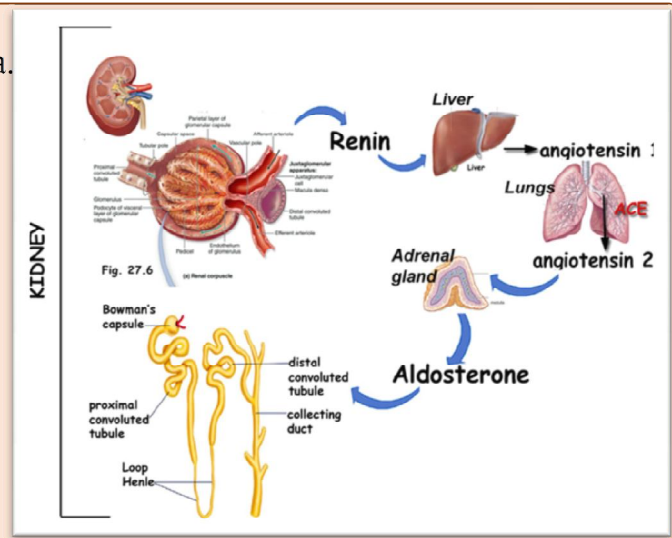
Physiology:- secreted by zona glomerulosa.
Increases Na and water reabsorption
Increases K, and H secretion in:-
DCT - Saliva - Sweat - Intestine

Factors affecting (regulations)

Stimulatory

Renin – angiotensin system activation
Increased K or Decreased Na
ACTH (only in stress)

Inhibitory



Aetiology:

1. Adenoma of zona glomerulosa
2. Hyperplasia of zona glomerulosa
3. Para-malignant

Clinical Picture: (3H:- HTN-HypoK-H excretion)

1. Hypertension : Mild Due To (Na& water) retention

Mild Hypertension:- due to:

- a) Nephrogenic diabetes insipidus secondary to hypokalemia.
- b) Renal escape phenomena ($\uparrow$ blood volume $\rightarrow \uparrow$ GFR $\rightarrow$ Polyurea)

2. Hypokalemia that manifests by :-

- a) Skeletal muscle weakness: flaccidity up to paralysis
- b) GIT: $\downarrow$ peristalsis, constipation up to paralytic ileus.
- c) Cardiac: Arrhythmia and ECG changes (prolonged PR interval, depressed ST segment, flat or inverted T wave and prominent U wave)
- d) Kidney: nephrogenic diabetes insipidus.
- e) Glucose intolerance
- f) Finally coma.

3. Alkalosis (Hydrogen excretion): which is exaggerated by intracellular shift of hydrogen with extracellular shift of K to compensate for K loss. Manifested as **tetany** due to decreased ionized calcium.

Investigations:

1- Hormonal assessment:- may be Selective adrenal vein sampling for aldosterone.

- Increased serum aldosterone level (N = 3-15 ng%)
- Serum rennin level is low (negative feedback)

2- Images- Abdominal sonar, MRI, CTscan (For detection of the cause)

3- hormonal effect:-

	<i>Increased</i>	<i>Decreased</i>
Blood	Na	K - Alkalosis (ph- HCO ₃)
Urine	K - Aciduria	Na

DD:- Secondary hyperaldosteronism

Primary hyperaldosteronism	2ry Hyperaldosteronism
Mild hypertension	Not a must hypertensive (except with RAS)
Mild or no oedema	Marked oedema in liver, renal and HF
Hypokalemia can be corrected by K intake	Hypokalemia cannot be corrected by K
↓ Rennin	↑ Rennin
Normal renal biopsy	Hypertrophy of juxta-glomerular apparatus.

Treatment:

1. Symptomatic treatment:

Diet: a- Increase K and reduce Na

2. Hormone antagonism:

- Spironolactone (200-600 mg/day)
- Triametrene or amiloride
- Metyrapone (11-B hydroxylase inhibitor)

3. Surgical removal of adenoma

Secondary hyperaldosteronism

Aetiology:

1. Renal ischemia:
 - Renal artery stenosis (RAS)
 - Malignant hypertension
 - Others : -HF -LCF - Nephrotic syndrome
2. Barter syndrome:- inherited defect in the thick limb of the loop of Henle.

Clinical Picture: As primary but with more marked edema

Investigations: As primary but with high serum rennin and dilutional hyponatraemia.

Treatment: As primary + ACEI (captopril 6.25-75 mg/day)

Cushing syndrome

Cortisol

Physiology:- secreted by zona fasciculata.

Action:-

A. Metabolic :

- **CHO:** Hyperglycaemia (anti-insulin:- increases gluconeogenesis and glycogenolysis)
- **Lipids:** lipolysis and redistribution of body fat to the trunk and the face from the limbs.
- **Proteins:** Catabolic (proteolysis of collagen in BVs wall, SC tissue, bone & muscles)
- **Minerals:** as aldosterone
- **Vitamins:** Anti Vit-D effect (prevents renal activation)

B. Anti action: Anti-inflammatory - Anti-allergic - Anti-stress - Anti-Vit. D

C. Androgenic like action

D. BM:

Increases RBCs, PMNLs	Decreases Lymphocytes, eosinophils
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E. Others:

- Potentiate the effect of catecholamines on BVs
- GIT: reduces the protective gastric mucus secretion
- Psychological effect

Factors affecting (regulations)

Stimulatory	Inhibitory
ACTH	Negative feedback

Circadian rhythm of ACTH:-

- ♦ Highest level: 4-9 AM (5-25 ug/dl)
- ♦ Lowest level: 9-12 PM (3-12 ug/dl)

Aetiology:

ACTH dependent (Cushing disease)	Non-ACTH dependent (Cushing syndrome)
Pituitary basophil adenoma (65%) (microadenoma) Ectopic ACTH secreting tumors: bronchogenic carcinoma, Carcinoids S. Exogenous ACTH	Adrenal adenoma or carcinoma Exogenous corticosteroids (Cushinoid)

Clinical picture:-

1- Type of patient:- Age: 30-40 years sex: females > males

2- Hormone effect:

A. Metabolic: (5)

- **CHO:** DM in 1/3 of cases (insulin resistant)
- **Lipids:** Deposition of fat in
 - Interscapular area (Buffalo hump)
 - Trunk (trunkal obesity + thin limbs = samboxa shaped)
 - Face: moon face, with fish mouth
- **Proteins:**
 - Muscle wasting and proximal myopathy
 - Osteoporosis with bone aches and pathological fractures



- SC tissue: delayed wound healing, rupture of SC collagen fibers along with mobilization of SC fat leads to reddish lines (**striae rubra then alba**)
- BVs: Rupture of BVs leads to easy bruising and prolonged bleeding time

➤ **Minerals:**

- Na and water retention:- **Hypertension** and edema
- Hypokalemia (mention clinical picture)
- Alkalosis:- Tetany

➤ **Vitamins:** Hypocalcemia with osteomalacia or rickets

B. Androgenic manifestations:

- **In males:** Baldness and ↑ of libido
- **In females:** amenorrhea, **hirsutism**, and **acne**

C. Anti-inflammatory: Reduced immunity with increased liability for infection with opportunistic organisms.

D. BM: Polycythaemia causing **plethoric face (RED MOON FACE)**, which becomes cyanosed in cold weather

E. Others: - GIT : Peptic ulcer
- Psychiatric depression

3- C/P of the cause:

- Pituitary Cushing: **hyperpigmentation** & may be increased ICT
- History of steroid intake in **cushinoid**
- Carcinoid syndrome in cases with paraneoplastic syndrome

Causes of death:- infection or cardiovascular complications

Investigations:-

1- Hormonal assessment

A- Static:-

- Serum **cortisol**:- Initially there is loss of circadian rhythm followed by persistent high level (N=5-20 ug%)
- Increased 24 hrs **urinary** excretion of free cortisol.
- Elevated 24 hrs urinary oxygenic steroid level (hormone end product)

B- Dynamic:- Dexamethazone suppression test (see below).

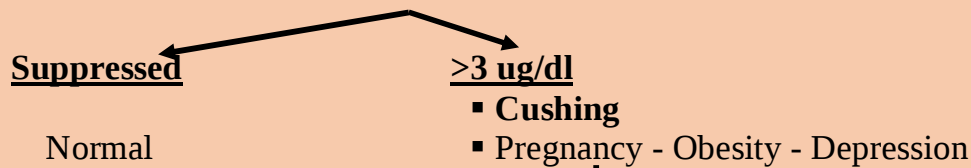
2- hormonal effect:-

	Increased	Decreased
Metabolic	S. glucose	
Minerals	S. Na - urinary:- K & aciduria	K - Alkalosis - Ca (Anti-Vit.D)
BM	Erythrocytosis- PMN leucytosis	Esinopenia, lymphopenia

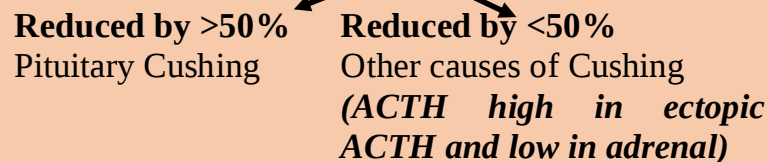
3- Images:- Abdominal/brain/chest = Sonar, MRI, CTscan (For detection of the cause)

Cause of Cushing syndrome:**A-Serum ACTH (N=60 pg/ml)****B-Dexamethazone suppression test****Step 1- Low dose test:**

- 0.5 mg dexamethasone/6 hrs for 48hrs
- Cortisol serum level measured before and at the end of the test:

**Step 2- High dose test:**

Dexamethasone 2 mg/6 hrs for 48 hr
Cortisol serum level before and after the test

**Treatment:-****1. Treatment of manifestations:**

- Correction of hyperglycemia (My need high doses of insulin)
- High protein diet
- Fluid restriction and diuretics
- K & Ca and Vitamins supplements
- Avoid trauma and surgery
- Proper treatment of infection

2. Treatment of the cause:

A. Pituitary Cushing:	B. Adrenal Cushing:
1. Surgical removal 2. Irradiation using yttrium-90. 3. Bilateral adrenalectomy 4. Reduction of tumor size:- bromocryptine , cyproheptadine.	1. Surgical removal followed by ACTH to activate the other atrophic gland 2. Metyrapone : 11 hydroxylase blocker (medical adrenalectomy). 3. Adrenal carcinoma is inoperable due to metastasis

Nelson syndrome: Bilateral adrenalectomy → loss of -ve feedback effect on pituitary adenoma secreting ACTH → ↑ size of tumor → ↑ ICP+ excess pigmentation.

Pseudo-Cushing

Cause: chronic alcoholism results in impaired metabolism of corticosteroids due to impaired liver function + direct effect of alcohol on cortisol or ACTH release

C\p and investigations: as Cushing

Treatment: stop alcohol intake.

Pharmacological uses of corticosteroids**Indications:-**

1. **CNS:** Bell's palsy, DS, ICP, myasthenia, Gullian-Barrie.
2. **CVS:** Rheumatic fever, myocarditis, and Dressler syndrome
3. **Blood:** immune hemolytic anemia, lymphoma
4. **Respiratory:** bronchial asthma, COPD, Hamman Rich, milliary TB
5. **Liver:** Lupoid hepatitis
6. **GIT:** Ulcerative colitis, Crohn's disease
7. **Renal:** glomerulonephritis, nephritic syndrome
8. **Collagen diseases** and vasculitis
9. **Allergic diseases:** anaphylaxis, angioneuritic edema, hay fever, eczema, and conjunctivitis
10. **Replacement therapy:** addisson disease, addissonian crisis
11. **Immunosuppression** in organ transplantation

Complications: Manifestations of Cushing syndrome (without pigmentation)

Hyper function of zona reticularis**Adrenogenital syndrome – Congenital adrenal hyperplasia**

Aetiology: Reduced cortisol secretion (A.R. deficiency of cortisol synthesis) will lead to increased ACTH→secretion of androgenic steroids (androstendione, testosterone, testosterone, and hydrogesterone)→virilizing syndrome.

Clinical picture:

	Males	Females
Pre-natal		Pseudohermaphrodism:- small vagina - big clitoris - big fused labia major
Post-natal	Precocious puberty: Macro-genito-mastia precox (muscularization, deepening of voice fused epiphysis & dwarfism but with small testicle and no spermatogenesis)	Virilism - amenorrhea - breast atrophy - dwarfism
After puberty		secondary amenorrhea - sterility - atrophy of external genitalia - enlarged clitoris.

Investigations:

1. ↑↑ACTH
2. ↑↑17-Hydroxy progesterone level
3. Increased urinary pregnanteriorol

Treatment: Glucocortecoid replacement

Pheochromocytoma (tumor of 10%)

Pathology:

- Tumor of chromaffin tissue
- 90% from adrenal medulla & **10% from other chromaffin tissue**
- 90% benign and **10% malignant**
- **10% is bilateral**
- **10% multiple tumors.**

Clinical picture:

1. Hormone effect (increased catecholamines):

- **Hypertension:** at first **paroxysmal** then it is persistent (1% of secondary causes of hypertension, 0.5% of severe hypertension).
- Papillary dilatation
- Tachycardia, arrhythmia
- Anxiety
- Sweating, dyspnea, vomiting

2. Complications:

- CNS: stroke secondary to hypertension
- CVS: IHDs (coronary spasm + HTN), cardiomyopathy (myo-necrosis)
- DM: due to insulin antagonism
- Sudden death due to arrhythmia

3. Associations:

- Neurofibromatosis - MEN-II - Hypertrophic Cardiomyopathy
- *Von-Hippel Lindau syndrome: CNS and retinal hemangioblastomas, renal and pancreatic cysts, and hypernephroma.*
- *Sturge Weber syndrome: CNS A-V malformation, and cutaneous angioma of the face.*

Investigations:.

1- Hormonal assessment

<u>Static</u>	<u>Dynamic</u>
S. catecholamines:- elevated (N=2-5mg/L)	<u>Suppressor test:</u> clonidine (α -blocker) injection IV 5mg→↓ of BP by 53/25 mmHg for 15 minutes
24hrs urinary Vallinyl mandelic acid (VMA) is elevated	Negative in pheochromocytoma

2- hormonal effect:- ECG, ECHO and blood glucose level

3- Images:- for detection of the cause

- CT, MRI or sonography of abdomen
- IVP may show indentation of the upper pole of kidney
- Aortography: to show arterial supply of the tumor.
- Isotoping scan:- **Metaiodobenzyl guanidine (MIBG)**

Treatment:

1. Hormone action: α -blocker (phenoxybenzamine 20-40 mg/day) followed by B-blocker (Propranolol 120-240 mg/day) or combined α and B blocker (labetalol)
2. Surgical removal of the tumor.

Hypo function of supra renal gland**Addison disease****Aetiology:****I- Primary Addison disease (80%): (Autoimmune + 4Ts+ ---)**

1. Autoimmune: The most common cause
Associated with other autoimmunes e.g. Type 1 DM, Addisonian pernicious anemia, thyroiditis, vitiligo.
2. TB: One of the most common causes
3. ttt - Surgical: Adrenalectomy with neglected replacement therapy
4. ttt - Drugs: Ketoconazole, rifampicin
5. Tumors & Infiltration: Hemochromatosis, amyloidosis, and sarcoidosis
6. AIDS: Secondary to CMV infection or due to treatment effect.

II- Secondary Addison disease (20%)

1. Sheehan syndrome
2. Panhypopituitarism

Clinical Picture:**I- Hormonal effect:- (3 Hypo & 3 Hyper)**

3 Hypo	1. Hypotension: (decreased cortisone & aldosterone) - Hypovolemia (Na loss) + loss of pressor response to catecholamines - Initially postural hypotension then persistent hypotension (BP<110) 2. Hypoglycemia: (decreased cortisone = anti insulin) - May lead to hypoglycemic coma without promontory symptoms. 3. Asthenia: (Hypo power) - ↓Cortisol → ↓glucose - ↓Aldosterone → ↓ Na - ↓Androgen → ↓ anabolic effect
3 Hyper	1. Hyper-pigmentation:- - ACTH is released in the form of pro-opio-melano-cortin - In primary Addison disease there is excessive release of ACTH. Color: Slate colored (Grey-brown) Site: - Exposed areas: face, neck - Scars of operations after the onset of the disease - Already pigmented areas: e.g. areola and nipple - Mucous membrane of the mouth and tongue (diagnostic) - Palm creases 2. Hyperkalemia:- 3. GIT: Anorexia, nausea, vomiting, diarrhea and abdominal pains

4. Infertility

II- **C/P of the cause**: e.g. TB, or other autoimmune manifestations e.g. vitiligo.

Investigations:**1- Hormonal assessment****A- Static:-**

- Low cortisol (N=5-20 ug%)
- Low Aldosterone serum level
- Low Hormonal end products urinary 17-oxygenic steroids & tetrahydroaldosterone
- **ACTH level:-**

Can differentiate 1ry and 2ry

<u>High ACTH</u> Adrenal cause (Primary Addison)	<u>Low ACTH</u> Pituitary cause (Secondary Addison)
➤ Adrenal antibodies ➤ Abdominal CT and X-ray may show calcification ➤ Investigation for sarcoidosis	➤ CT skull ➤ Other hormones e.g. TSH, Prolactin

B- Dynamic:- Stimulatory test : (ACTH stimulation test).**A. Synacthen test**

- Synacthen (synthetic ACTH) injection
- Measuring plasma cortisol before and 30 and 60 minutes after injection
- Normally cortisol should increase 7-20 ug%
- **Result:**
 - Failure to rise indicate primary or secondary Addison
 - Failure to rise after higher doses of ACTH ➔ **Primary Addison**

2- Hormonal effect:-

<u>Defective</u>	<u>Increased</u>	<u>Decreased</u>
<u>Cortisol</u>	Ca + lymphocytosis, eosinophilia	Glucose + RBCs + leucopenia
<u>Aldosterone</u>	- Serum K & Acidosis - Urinary:- Na	- Serum Na - Urinary:- K

3- Images:- Abdominal/brain/chest = Sonar, MRI, CT-scan (For causes)**Differential diagnosis:**

- 1- Other causes of **generalized pigmentation**:
 - Racial
 - Familial
 - Sun exposure
 - Hemochromatosis
 - Pregnancy
 - Contraceptive Pills
 - Addison disease
 - Pituitary Cushing
- 2- Other causes of **hypotension**
- 3- Other causes of **hypoglycemia** and **asthenia** e.g. malabsorption S., CRF, pellagra
- 4- Other causes of **hyperkalemia**
- 5- Primary from **secondary Addison** (mention)

Treatment:**I- Symptomatic**

Diet rich in: CHO, Protein, Na with low K

II- Hormone replacement:

- **Oral hydrocortisone:** 20 mg in the morning & 10 mg at night
- The dose should be increased in stress e.g. trauma, infection or surgery
- **Fluocortison:** 0.1-0.2 mg/day if **BP** is still low with cortisol replacement.

III- Treatment of the cause: e.g. hemochromatosis, TB.

Addisonian crisis

Definition:- one of the medical emergencies characterized by acute adrenal failure or hypocortisism

Aetiology:

1. Primary causes:

A. Acute from the start:

- Meningococcal septicemia (Waterhouse-Friedrichsen syndrome)
- Sudden withdrawal of chronic steroid treatment
- Hemorrhage in the gland:- after anticoagulant toxicity or in breech delivery
- Thrombosis of adrenal veins as in purpura, burns, DIC or pregnancy.

B. Acute on top of chronic:

- Patient with Addison disease exposed to stress e.g. trauma, infection, or surgery without adequate hormone replacement.

2. Secondary causes:

- a) Pituitary apoplexy: hemorrhage in pituitary adenoma.
- b) Surgical removal without replacement therapy
- c) Panhypopituitarism: when treatment starts with **Thyroxin before cortisone**

Clinical Picture:-

- a) Severe hypotension (**shock** = not corrected with saline or vasopressor)
- b) Hypoglycemia up to **Coma**
- c) Severe weakness up to confusion
- d) Skin desquamation
- e) Severe nausea, vomiting and diarrhea with abdominal pain (**acute abdomen**)

Investigations: (manage the patient at first)

As Addison disease after stabilization

Treatment:

1. Symptomatic ttt:

- **Fluids:** -1.5 L **glucose** 10% -1.5 L **Saline** (hypertonic saline) over 30-60 min

2. Hormone replacment:

- Hydrocortisone 200mg IV bolus ➡ 100 mg/8hrs infusion
- Desoxycorticosteroid acetate 5-10 mg IM if shock is persistent.

3. Treatment of the cause e.g. infection

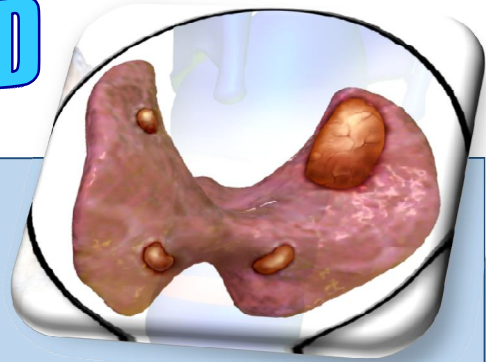
Other types of adrenal hypofunction:

1. Hyporeninimic hypoaldosteronism:

Aetiology: Diabetic nephropathy, interstitial nephritis, obstructive nephropathy.

2. Hyperreninimic hypoaldosteronism: defect in z.glomerulosa → ↓aldosterone → ↑renin

3 PARATHYROID GLAND



Calcium metabolism:

- Total body content 1100 gm, mainly in bone and teeth
- Serum calcium 9-11 mg%

Non diffusible portion (45%)

- Protein bound
- Acts as a reservoir

Diffusible portion (55%)

ionized
50%
Active form

Non-ionized
5%
Ca citrate,
bicarbonate, PO₄

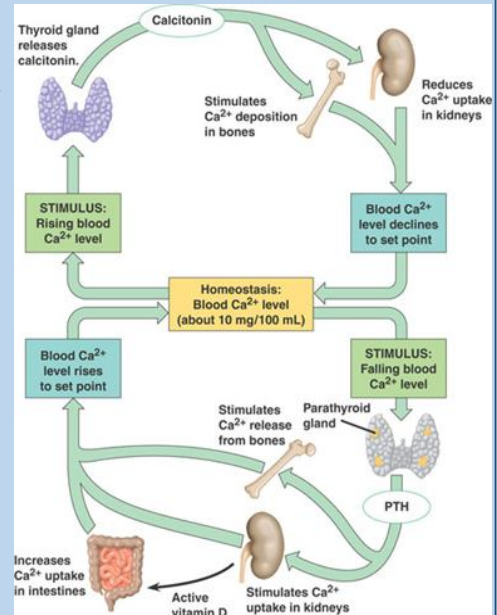
Function:

1. Blood clotting
2. Excitability of nervous and muscular tissues
3. Muscle contraction
4. Cardiac function: rhythmicity and contraction
5. Formation of intercellular cement substance
6. Secondary intracellular messenger

Regulation :

Ca is absorbed under the control of:

- | | | |
|---|----------------------|--|
| <ul style="list-style-type: none"> ➤ PTH ➤ GH ➤ Thyroxin ➤ Acidity ➤ Vit C & D | <p>Ca absorption</p> | <ul style="list-style-type: none"> ➤ Phytate ➤ Phosphate ➤ Cortisol |
|---|----------------------|--|



Ionized Ca and protein-bound Ca can be affected by acid-base balance:

- Acidosis increase ionized Ca
- Alkalosis decrease ionized Ca

Serum Ca-P solubility product kept constant around 40.

1- Parathormone hormone:

Increases serum Ca level by:

- Increase Ca absorption from **intestine** indirectly through Vit. D activation.
- Increase Ca reabsorption from the **kidney** but increases P excretion .
- Increase the activity of **osteoclasts** ➔ increase Ca mobilization from bone.

Factors affecting (regulations):- stimulated with Hypocalcemia but needs Vit D and Mg

2- Calcitonin: Secreted by parafollicular C cells of thyroid glands.

- Increase Ca & P uptake by the bone.

3- Vitamin D :- Produced in SC tissue by UV light on cholesterol or Vit D in diet.

Increase Ca absorption from the intestine.

Bones: in Rickets it increases Ca deposition in bone while in normal cases it causes Ca resorption

Kidney: in small doses = P retention - in large doses = P excretion .

Stimulates differentiation and inhibits proliferation of **keratinocytes**.

Inhibits the production of gamma interferon and iL-2 by **monocytes**.

Hyperparathyroidism

Aetiology:

1ry (80-85%)	Adenoma of parathyroid gland (may be a part of MEN I) Parathyroid carcinoma is rare
2ndry	Chronic hypocalcemia (e.g. malabsorption syndrome or CRF) with secondary hyperplasia of parathyroid gland
Tertiary	Prolonged secondary hyperparathyroidism will lead to adenomatous transformation (hyperplastic changes)
Paramalignant	as oat cell carcinoma of the lung

Clinical Picture:

1- Hormonal effect:-

Ca mobilization from bone:

- **Osteoporosis:** bone aches, pathological fractures (heal rapidly secondary to hypercalcemia).
- **Bone cysts** (Osteitis fibrosa cystica).
- Premature loosening of the **teeth** due to resorption of lamina

On kidney:

- **Polyurea (Ca diuresis)** with Polydipsia and thirst.
- **Stones:** bilateral, multiple, recurrent, and presents by colics, haematuria, recurrent urinary tract infection and CRF.
- **Nephrocalcinosis:** due to metastatic calcification ends with CRF

Hypercalcemia results in:

- **CNS:** apathy, drowsiness, malaise and personality changes
- **Eye:** band keratopathy (calcification of cornea)+ conjunctival injection
- **CVS:** bradycardia and short Q-T ± HTN
- **GIT:** - Constipation with hard stools
- Acute pancreatitis - Peptic ulcer, nausea and vomiting
- **Renal:** Polyurea and polydipsia (Nephrogenic diabetes insipidus) & nephrocalcinosis.
- **Muscles:** Hypotonia and waddling gait.
- **Joint:** Chondrocalcinosis (**pseudogout**)
- **Skin:** Dry and pruritis

2. C/P Of cause: e.g. CRF in

Investigations:

1- Hormonal assessment:-

- Elevated Parathyroid hormone
- Urinary C-AMP increase: **Characteristic** of hyperparathyroidism

2- Hormonal effect:**a) Serum Ca - P - alkaline phosphatase**

	Cause	Ca (9-11 mg%)	P (3-4.5 mg%)	Alkaline Ph.
Primary	Adenoma or PEA	+	-	+
Secondary	a) Malabsorption	-	-	+
	b) CRF	-	+	+
Tertiary	a) Malabsorption	+	-	+
	b) CRF	+	+	+

b) Kidney:

1. ↑Urinary 24 h. Ca: (normally 150 mg /24 h)
2. ↑Urinary 24 h. P. : (normally 1 gm /24 h)
3. Renal X-rays: Stones and nephrocalcinosis

3- Images:- (bone):

1. Subperiosteal erosion of phalanges (especially middle phalanges)
2. Resorption of lamina dura of teeth
3. Osteoporosis of bones manifested by:
 - God fish spine : soft spine & indentation of the vertebral bodies by discs.
 - Ground glass bones : poor calcification.
 - Mottling of skull (pepper – pot skull)
 - Milkman pseudo fracture or looser zone : a zone of radiolucency extending 1 cm into bone from surface due to decalcification around nutrient artery.
4. Bone cysts: osteitis fibrosa cystica generalisata.

**bone cysts****3- Detection of the cause:**

- Renal function tests, investigation for Malabsorption syndrome.
- Radioisotopic scanning of parathyroid using thallium & technetium.
- Steroid suppression test: "Dent test"
 - Hydrocortisone 40 mg orally 8 hourly for 10 days
 - lowers serum Ca in hypercalcemic states other than hyperparathyroidism (cortisone- ↓ action of Vit D).

DD: Hypercalcemia**I- ↑Ca intake:**

- Milk alkali syndrome "excess alkali or ingestion antacid for ttt of peptic ulcer"
- Over treatment of hypocalcemia

II- Increase Ca absorption:**a) Endocrinal**

1. Hyperparathyroidism (1ry, 3ry, ectopic – not 2ry)
2. Acromegaly
3. Thyrotoxicosis
4. Addison's disease
5. Vit-D intoxication, chronic granulomas (T.B., sarcoidosis) due to secretion of α -1 hydroxylase enzyme.

b) Idiopathic: idiopathic hypercalcemia with nephrocalcinosis**III- Increased mobilization from bone:**

1. Hypercalcemia of malignancy (e.g. multiple myeloma, lymphoma): 2ry to

a) Bone metastases**b) Secretion of hypercalcemic substances as:**

*PTH like. - 1,25 DHCC like - Interleukin 1 (IL1) - Tumor necrosis factor (TNF)
Osteoclast activating factor "OAF" especially in multiple myeloma*

2. Prolonged immobilization: HF, fractures, post operative

IV- Decreased calcium excretion by kidney:

1. Familial hypocalciuric hypercalcemia: benign AD symptomless disease.
PTH level is normal.
2. Thiazides, lithium

Acute Hypercalcemia

Definition: Emergency condition characterized by elevated serum $\text{Ca} > 12\text{-}13 \text{ mg\%}$

Clinical Picture:

- | | | |
|--------------------|----------------------|---------------------|
| ♦ Nausea, vomiting | ♦ Polyurea, nocturia | ♦ Drowsiness & coma |
|--------------------|----------------------|---------------------|

Treatment of Hyperparathyroidism & Hypercalcemia:-**I- Symptomatic treatment:-**

1. Decrease **intake**: avoid Ca in drugs or food (e.g. milk)
2. Decrease **absorption**: phosphate, phytate
3. Increase **loss**.
 - a) **Fluids** in excess to correct dehydration & wash out Ca in urine
 - b) **Furosemide** diuretic (**not thiazides**) - dialysis in severe cases
 - c) Chelating agent:- **EDTA** - Oral cellulose **PO4** 15mg/day
IV **PO4** infusion lower Ca rapidly by causing microscopic precipitation of Ca phosphate in soft tissue (**dangerous**)

II- Hormone antagonism:

- a) Precipitate in bone: **Calcitonine** IV amp. 10-25 ug/kg
- b) Hydrocortisone (--Vit D action)

- c) **Indomethacin**: especially in **malignancy** (prevent PG. mediated Ca release from bone)
- d) Drugs inhibiting **osteoclast** activity: of choice in hypercalcemia of **malignancy**
 - **Biphosphonate**: Pamidronate IV infusion (in hypercalcemic crisis)
 - **Mithramycin**: cytotoxic drug-25 Ug/kg IV infusion

III- Surgical removal of parathyroid followed by Ca & Vit-D to prevent tetany (Hungary bone syndrome)

Hypo-calcemia (Tetany)

Definition: Increased neuromuscular irritability due to decreased ionized Ca or Mg

Aetiology:

I- Hypocalcemia (Quantitative defect):

- A. *Diminished Ca intake : starvation, dysphagia*
- B. *Diminished Ca absorption:*
 - 1. Hypoparathyroidism:
 - Surgical removal
 - Autoimmune destruction
 - Goiter: diversion of blood supply to the enlarged thyroid gland.
 - Di-George syndrome: congenital absence of thymus and parathyroid
 - Tetania neonatorum (intraglandular hemorrhage)
 - 2. Deficiency of **Vit D**: rickets or osteomalacia
 - 3. Myxedema, panhypopituitarism, Cushing
 - 4. Gastrectomy, atrophic gastritis, and gastric carcinoma
 - 5. Malabsorption syndrome
- C. *Increased Ca loss in urine:*
 - ♦ Loop diuretics
 - ♦ Renal rickets
 - ♦ CRF (associated acidosis usually increases **ionized** Ca)
- D. *Increased Ca precipitation in tissues:*
 - ♦ In acute pancreatitis
 - ♦ Hungry bone syndrome following parathyroidectomy
 - ♦ Over treatment by calcitonin, phosphate or biphosphonate

II- Alkalosis (Qualitative defect with reduced ionized calcium)

- Respiratory: encephalitis lethargica, high altitudes, hysterical
- Metabolic: vomiting, Conn's syndrome, diuretics
- Citrated blood in massive blood transfusion

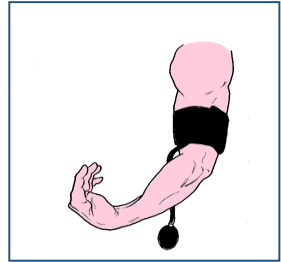
III- Mg deficiency:

- Hypoparathyroidism
- Excessive diuretics
- Malabsorption syndrome

Clinical Picture:**I- Latent Tetany: (serum Ca 7-9 mg%):**

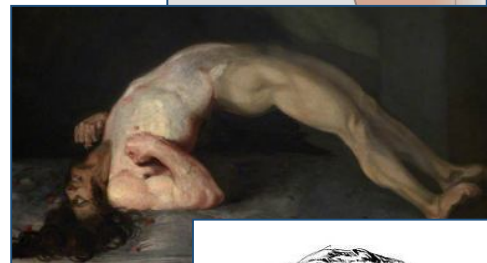
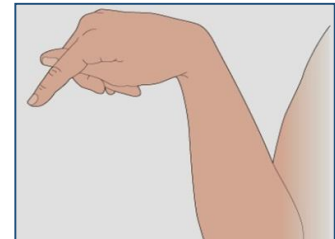
There are no spontaneous manifestations but it can be induced (provocative tests):

Provocative tests

Chovestek's	- Tapping of facial n. in front of the ear causes facial muscle contraction - Tapping the peroneal nerve over the of fibula causes peroneal muscle contraction	
Trousseau's	Sphygmomanimeter inflation above systolic pressure for 5 minutes → Carpal spasm.	
Erb's	Current < 4mA causes muscle contraction (normally at least 8 mA)	

II- Manifest Tetany (Ca <7 mg%):-**1. Muscle spasm in the form of:**

- Spasm of the facial muscle (**risus sardonicus**)
- Spasm of jaw (**trismus**)
- Spasm of larynx (**Laryngismus stridulous**)
- Spasm of the diaphragm (**hiccough**)
- Spasm of the back muscles (**opithotonus**)
- Wall of the urinary bladder (**enuresis**) or the sphincter (**retention**)
- **Carpopedal spasm**, muscle twitches & convulsions

**2. Effect on ectodermal structures:-**

- Nails: Loss of luster & brittle
- Skin: desquamation, atrophy, roughness, alopecia, and monilial infection
- Hair: Premature loss of hair
- Lens: cataract
- Teeth: Hypoplastic, transverse furrows and punctuate holes if the condition develops before formation of permanent teeth
- GIT: Malabsorption due to desquamation of GIT mucosa

**3. C/P of the cause: e.g. primary hpoparathyrodism:-**

- Calcification of basal ganglia (Parkinsonism)
- Pseudotumor cerebri

Investigations:**In Hypocalcemia:**

- ↓ Serum Ca (N=9-11 mg%)
- ↑ Serum P (N=3-4.5 mg%) in hypoparathyroidism
- Urine: ↑Ca, ↓P+
- Prolonged Q-T
- Of cause: high parathormone level in all cases other than hypoparathyroidism

In alkalosis:

- High blood pH
- Normal total Ca & P, but low ionized Ca level

In hypomagnesaemia: ↓ serum Mg (N=1.7-2.4 mg%) + Resistant hypokalemia

Treatment:

1. In acute attacks: Ca gluconate 10 ml (10 mg%) **SLOWLY** over 10 minutes
2. Treatment of the cause:
 - In hypocalcemia:
 - ♦ Oral Ca lactate 2 gm TDS
 - ♦ Active Vit D (1-25 DHCC, or 1-alpha HCC) 1 ug daily
 - ♦ Thiazide diuretics to decrease Ca excretion in urine
 - In Alkalosis: treatment of the cause
 - In hypomagnesaemia: oral Mg

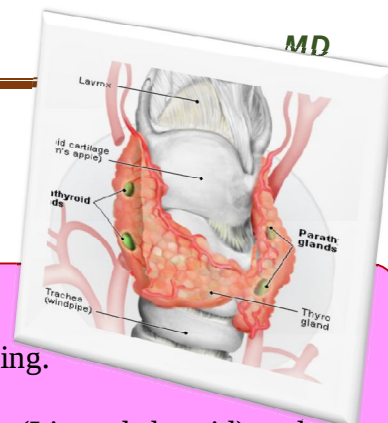
➤ **Pseudo-hypoparathyroidism:**

- **Cause:** End organ unresponsiveness due to non-functioning receptors
- **C/P:** Hypocalcemia + short 4th & 5th metacarpals & metatarsals + MR + short.
- **Investigations:** decreased urinary cAMP + phosphaturia

➤ **Pseudopseudo-hypoparathyroidism: as above but without hypocalcaemia**

4

Thyroid Gland



Anatomy: Formed of two lobes connected by an isthmus.

Attached to the thyroid cartilage, and thus moves on swallowing.

Embryology: arises from the base of the tongue

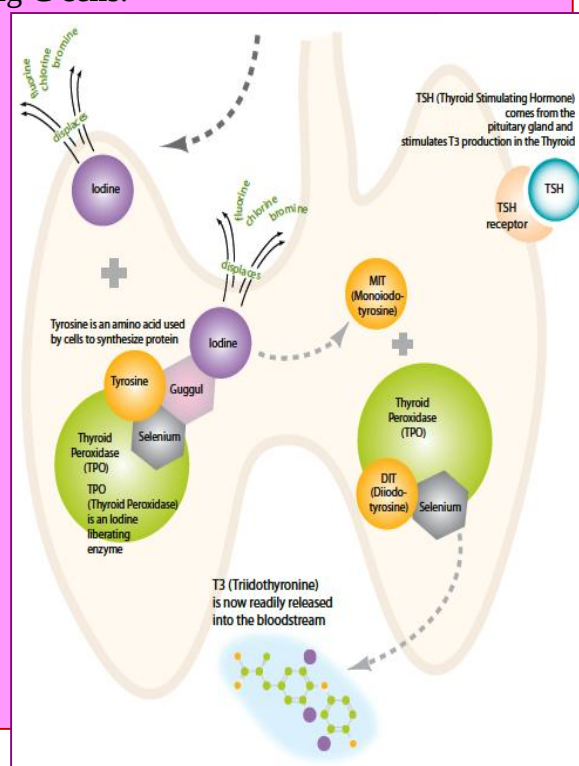
Remnants can sometimes be found at the base of the tongue (Lingual thyroid) and along the line of descent.

Blood supply: rich blood supply from superior and inferior thyroid arteries and others.

Histology: consists of follicles lined by cuboidal epithelioid cells. Inside the follicles there is colloid, which is an iodinated glycoprotein (thyroglobulin), between which are parafollicular cells containing calcitonin-secreting C cells.

Thyroxin synthesis steps

- ♦ Iodine trapping
- ♦ Binding Tyrosine and iodine to form mono-and di-iodotyrosine
- ♦ Coupling of two molecules of di-iodotyrosine to form T4 or mono and di-iodotyrosine for forming T3
- ♦ Storage as thyroglobulin
- ♦ Release after action of protease enzyme on Thyroglobulin
- ♦ Circulating hormone is either free (active) or bound to thyroxin binding globulin, pre-albumin and albumin



Thyroxin

- ♦ Increases oxygen consumption and basal metabolic rate
- ♦ **CHO:-** hypoglycemic effect even with glycogenolysis
- ♦ **Protein:-** catabolic effect
- ♦ **Lipid:-** Decreases cholesterol
- ♦ Enhances tissue responsiveness to **catecholamine**
- ♦ Hepatic conversion of **carotene** to vitamin A
- ♦ Stimulates **skeletal, mental and sexual** development

Factors affecting (regulations)

Stimulatory	Inhibitory
TRH (hypothalamus) stimulates the release of TSH (pituitary).	T3 has negative feedback effect on the pituitary and the hypothalamus

Thyrotoxicosis

Aetiology:-

1. **Primary** graves' disease
2. **Secondary** toxic nodular gaiter
3. **Plummer's** disease: solitary toxic adenoma secreting T4
4. TSH producing **pituitary** tumor (rare)
5. **Ectopic** thyroid tissue: e.g. choriocarcinoma
6. Thyroiditis: Hashimoto "**transient thyrotoxicosis**" viral" De Quervain disease"
7. Exogenous iodine" jod-Basedow phenomenon"
8. Iatrogenic : excess TSH, T4, amiodarone.

Primary Thyrotoxicosis "Grave's Disease"

Aetiology:

Autoimmune disorder as evidenced by:

1. Association with HLA B8, DR3,
2. **TSI**:- Thyroid stimulating immunoglobulin act as TSH
3. Recently **TRA** (TSH receptor antibody)
4. Association with other **autoimmunes**:- thymic enlargement, splenomegaly, lymphadenopathy, myasthenia graves, SLE, pernicious anemia, and Addison's disease.

Clinical Picture:

Type of patient:-

Female-to male ratio is 8-1 - Occur in **middle age** (30-50 y)

General & metabolic:-

- **Polyphagia with loss of weight.**
- Intolerance to **hot weather.**
- Progressive muscle **weakness**

- **Polyurea** may be present due to: *Increase water intake (polyphagia) - Increase water production (metabolism) - Increased renal blood flow*

- **may be Hyperglycemia** due to increased glucose absorption and insulin antagonism, but may be hypoglycaemia as increasing BMRs

Gland:- toxic goitre

- Thyroid gland diffusely **enlarged** & firm
- Systolic **bruit** may be present due to increased vascularity
- Examine also for retrosternal extension

Gonadal:- menstrual disturbance, infertility

GIT:

1. Increased appetite with loss of **weight**
2. **Diarrhea** & even steatorrhea
3. Generalized **lymphadenopathy** & **splenomegaly**

C/P:- 6G + eye + CNS

General

Gland

Gonadal

GIT

جلدSkin

CVS

Neurological

Eye

Skin:

- **Warm flushed** (salmon pink) - excess **sweating** (VD and hypermetabolism)
- **Pigmentation** is common but vitiligo occurs in 7% of cases
- **Hair**: thin, with premature falling and graying
- **Nail**: recession of nail bed base onycholysis "Plummer's nail"

Pretibial myxoedema: tender itchy swelling over the shins of tibia be due to LATS. It may be accompanied by clubbing of fingers (thyroid acropachy) & Exophthalmos.

Cardiovascular system: marked in old age

Palpitation is the commonest symptom due to

- Tachycardia (sleeping pulse > 100/ min)
- Hyperdynamic circulation
- Arrhythmia
- Neurosis

Arrhythmia: any arrhythmia except heart block. The commonest is AF.

Hyperdynamic circulation: due to high systole (forcible heart) & low diastole (arteriolar VD) leading to water hammer pulse, big pulse pressure, functional systolic murmur & ending in **high CO heart failure**.

Neurological manifestations:

1. **Psychic**: restlessness, anxiety, insomnia & rarely mania occur.

2. **Organic**

- Fine **tremors** of outstretched hands & unsupported tongue
- **Myasthenia gravies** (auto-immune disorder)
- Thyrotoxic **myopathy**: 2 forms
 - Chronic;- involving proximal muscles - Acute:- involving bulbar muscles

Eye:- Ophthalmopathy:-

Non-Infiltrative:- increased thyroxin leads to retraction of Muller's muscle. (not specific to Grave's)	Infiltrative:- auto-antibody called exophthalmos producing substance (EPS) leads to infiltration with myxomatous tissue in retrobulbar space, extraocular muscle & lacrimal gland
1. Stellwag's :- Staring look + Infrequent blinking	1. Exophthalmos:- uni/bi-lateral, may occur before thyrotoxicosis " ocular Grave's "
2. Dalrymple's :- rim of sclera above cornea.	2. Injected conjunctiva
3. Von Grafe's : lid lag on looking down	3. Swelling of eye lids & of lacrimal glands
4. Rosenbach's : fine tremors on closure of eye lids.	4. External ophthalmoplegia: paresis of oculomotor muscles
5. Slight exophthalmos: retracted upper lid	a) Moebius sign : lack of convergence due to weak medial recti
	b) Joffroy sign :- Lack of forehead corrugation on looking upwards.
	c) Ruler test is diagnostic

Malignant exophthalmos with papilledema & corneal ulcers

Uncommon Forms of Thyrotoxicosis

1. T3-Toxicosis:

- Cause: It may be due to excess conversion of T4 to T3 in tissues
- C/P: It appears in old patient & its main features are cardiac (AF & HF) together with severe muscles weakness, diarrhea, vitiligo of hands & feet.
- Investigations: T4 level & radioiodine uptake are normal. High T3 level is diagnostic.

2. Masked or apathetic Thyrotoxicosis:

- Cause: due to depletion of catecholamine in long standing cases
- C/P: Occure in old people where the general features of thyrotoxicosis are replaced by apathy, weakness, cool dry skin simulating myxoedema.

3. Congenital thyrotoxicosis: transmitted thyrotoxic mothers to babies (self limited)

4. Myasthenic form: associated myasthenia gravies with thyrotoxicosis

5. Monosymptomatic form: one of the manifestations is predominates e.g. thyro-cardia

Investigations:

1- Hormonal assessment

1. Total T4 & T3 : increased (inaccurate)

- Measurement of free + protein bound hormone
- T4 = 4-12 ugm% - T3=70-170 ngm%
- Disadvantage: affected by change in thyroxin binding protein :TBP"
TBP:- decrease in:- LCF - nephritic - malnutrition – thyrotoxicosis
- increase in:- estrogen (pregnancy, C. pills)–phenothiazines– myxoedema

2. Free T3 & T4 : increased (the most accurate)

- Measured by radioimmunoassay
- Normally:T4 : 1.6 ngm % -T3: 0.4 ngm%

3. TSH level:

- Normally: 0.5 -5 mcu/ml
- It increases in : primary hypothyroidism, TSH producing tumor.
- It decreases in : secondary hyothroidism, thyrotoxicosis.

4. T3 resin uptake: is low

Radioactive T3 is added to the patient serum where it is fixed to the binding sites of TBP not already saturated. The remaining unabsorbed radioactive T3 is then absorbed on to a resin & the radioactivity of resin is measured, (Normally 25 – 35%)

5. Free thyroxin index T4 x T3 resin uptake: high > 11.5

it is now replaced by measurement of free T3 & T4.

6. T3 suppression test: measurement of radioactive iodine uptake (RIU) before & after giving T3. It is used to diagnose mild hyperthyroidism.

7. Others (for the Cause):

1. Needle aspiration biopsy
2. Thyroid antibodies
 - Thyroid receptor antibodies: TSI, LATS or LATSP (positive in Grave's).
 - Thyroid microsomal antibodies: in **Hashimoto's** disease

2- Hormonal effect:-

Increased:- cholesterol - calcium - $\pm$ glucose - Basal metabolic rate "BMR": increases in thyrotoxicosis (not practical).

3- Images:-

- Thyroid ultrasound - Ct-scan:-
- Thyroid scan:- : using I_{131} or 99 mTc with Gamma camera
Differentiate cold (malignant) hot & neutral nodule
Differentiate Grave's (diffuse), toxic nodule & multinodular goiter
Detect retro-sternal goiter or ectopic thyroid tissue
- Radioiodine uptake: increases in thyrotoxicosis

Differential Diagnosis:

1. **Anxiety** neurosis: cold hands, normal pulse
2. **Increase appetite with loss of weight**: DM, parasites, malabsorption
3. **Hyperdynamic** cases: Anemia, Beri-Beri, A-V fistula, hypoxic corpulmonale.
4. **Muscle** diseases: myopathies, myasthia gravies
5. **Primary from secondary** forms (see table below)
6. **Monosymptomatic** form.

	1ry thyrotoxicosis	2ry Thyrotoxicosis
1. Cause	Auto-immune	On top of nodular goiter or adenoma
2. Age of onset	30-50	>50 Y
3. Thyroid	Diffusely enlarged	Nodular – or single nodule
4. CVS	Mild	Severe
5. CNS	Severe	Mild
6. Exophthalmos	Infiltrative	Absent
7. Monosymptomatic	Uncommon cases	Common
8. Treatment	Usually medical	Usually surgical

Treatment:**I- Proper treatment:-**

Table page 38

- 1- Medical
- 2- Radio-iodine
- 3- Surgical

II- Treatment of Complications:

A. Ocular Complications: in addition to usual treatment add:

1. Protect eye by ointment, and sun glasses.
2. Guanethedine 5% eye drops or B-blocker to lid retraction, & conjunctival injection
3. Lateral tarsorrhaphy
4. Severe cases: prednisone 120 mg /day, or decompression operation (supraorbital deroofing called called Nafziger's operation)

B. Pretibial myxoedema: Local betamethazone cream

C. Heart Failure:

1. Bed rest, salt restriction, digitalis, diuretics.
2. Carbimazol till the patient becomes euthyroid, then stop for 4-7 days & give radio-iodine, then restart carbimazol for 3-4 months.
3. Persistence of AF after control of thyrotoxic state need B, blockers or DC shock.

D. Treatment of thyrotoxic crisis (see later)**Thyrotoxic Crisis**

(Thyroid storm)

Definition:- Life-threatening complication of severe thyroid activity with about 10% mortality**Cause:-**

- a) Lack of preoperative preparation
- b) I-131 in thyrotoxic patient
- c) Stress, infections in untreated patients

Clinical picture: may be masked by B-blocker

1. **Fever:** hyperpyrexia –Temperature may reach $> 41^{\circ}\text{C}$
2. **CNS:** marked irritability. In old age there is apathy, bulbar palsy from myopathy.
3. **CVS:** tachycardia, acute HF, arrhythmia.
4. **GIT:** nausea, vomiting diarrhea. Later collapse, shock, delirium up to coma.

Treatment: emergencya) Anti-thyroid:

1. **Carbimazol** or better **propyl-thiouracil:** 40 mg at the start, then 10 mg/6 h.
2. **NaI or KI:** 500 mg/8 h infusion to decrease the release of thyroid hormones
3. **Propranolol:** 0.5 mg IV then 0.5 mg/min till a max. of 5 mg for tachyarrhythmia
4. **Dexamethazone or hydrocortison:** ↓release of T4 - ↓conversion of T4 to T3

b) Symptomatic:

1. Chlorpromazine: as sedative & hypothermic
2. Antipyretics (acetaminophen not aspirin) & foment: for fever
3. Digoxin & diuretics for AF & HF
4. Nasogastric tube for bulbar palsy, nausea, vomiting.

c) Treatment of cause & precipitating factor: e.g. antibiotics for infection.**Thyrotoxicosis in Pregnancy:**

1. 2 main drugs:- propylthiouracil (PTU) and methimazole
2. Radioactive iodine is absolutely contraindicated (teratogenic – carcinogenic)
3. Surgery is indicated if: Poor drug response or side effect.
4. TSI cross the placenta & stimulate fetal thyroid:- So immediate infant check should be done to diagnose & treat neonatal thyrotoxicosis.

	Medical	Radio-iodine	Subtotal Thyroidectomy
Indication	1. Primary thyrotoxicosis 2. Secondary thyrotoxicosis:- - pre-operative preparation - inoperable. 3. Thyrotoxicosis with pregnancy 4. For complications e.g. arrhythmia	1. Failure of medical ttt 2. Patient unfit for surgery 3. Patient age > 40 y . 4. Recurrence after thyroidectomy 5. Toxic adenoma	1. Secondary thyrotoxicosis 2. Failure of medical ttt in primary cases 3. Huge goiter - retrosternal 4. Suspicion of malignancy
C.I.	1. Retrosternal goiter or large one (TSH rise will increase pressure symptoms and exophthalmos) 2. Suspicion of malignancy	1. During pregnancy, lactation, childhood 2. better not in child bearing period) 3. Huge goiter & retrosternal goiter	1. malignant exophthalmos
Methods	1. Nutritious diet, proteins, vitamins 2. Sedative & tranquilizers: diazepam, phenobarbitone 3. Propranolol (inderal): B-blocker relieve systemic effects mediated by sympathetic over tonus e.g. arrhythmia ➤ Dose: 40 mg t.d.s. ➤ Side effects(look cardiology) 4. Antithyroid drugs: interfere with binding of I with Tyrosine a) Thiouracils: had in addition the ability to inhibit conversion of T4 to T3 in tissues Methyl-thiouracil: 200 mg tds then reduce dose after 4-6 weeks to 100 mg tds Propyl-thiouracil: 100 mg tds then reduce dose after 4-6 weeks to 50 mg tds b) Carbimazol (Neomercazol): 20 mg tds to be reduced after 4-6 weeks to 10 mg tds Duration of ttt: 12-24 months Follow up by: CBC (to exclude aplastic anemia) & TSH (doses adjusting) Side effects: - Allergy: fever, rash, generalized lymphadenopathy, arthritis. - Others: GIT . upset, cholestatic jaundice, SLE (drug induced) - Hypothyroidism especially in newborn with thyrotoxic mother	Side Effects: • Hypothyroidism • BM inhibition • Fetal anomalies if taken in pregnant females • ↑Incidence of thyroid or other malignancy (not proved)	Preoperative preparation: Lugol's iodine (5% I ₂ in 10% KI 15 drops TDS for 10 days. It reduces size & vascularity of gland
	- Granulocytopenia: sore throat, fever - Goitre due to ↑TSH - Relapse: on sudden stoppage		

Hypothyroidism

Cretinism

Aetiology:-

1. Congenital absence of thyroid gland
2. Congenital enzymatic defect in synthesis of T4 "cretinoid goiter"
3. Pendred's syndrome: cretinism + congenital deafness
4. I deficiency (endemic cretinism)
5. Excess antithyroid drugs during pregnancy

Clinical picture:

1. CNS: mental retardation, slow speaking
2. General features
 - Face: puffy eye lids, depressed nose, big lips, protruded tongue, delayed dentition
 - Hands: square-shaped, with short fingers
 - Disproportionate dwarfism: height > span
 - Delayed walking & waddling gait
 - Hypothermia
3. CVS: bradycardia, low voltage ECG with flat T-wave
4. Skin : dry, cold, scaly, with SC myxoedematous tissue deposition in hands, face & supraclavicular region.
5. Muscle: weakness, constipation, pot-belly abdomen



Investigations:

1. Low T3 T4, FT3, FT4 levels
2. **TSH** level: high "characteristic"
3. Serum cholesterol: high
4. X-ray carpal bones: delayed appearance of ossification centers.

Juvenile Myxoedema

1. Age of onset is 4-12 years
2. Mentality is normal
3. Main presentation is dwarfism
4. x-ray: epiphyseal dysgenesis (multiple stippled foci instead of a single focus of ossification in epiphysis)

Myxoedema

Aetiology:-

A. Primary:

1. Endemic myxoedema: prolonged I₂ deficiency
2. Goitrogenous substance: cabbage, I₂ containing cough mixture, PAS, Amiodarone
3. Destruction of thyroid gland
 - a) **Primary** idiopathic atrophy; auto-immune (circulating ab)
 - b) **Hashimoto's disease** "Lymphadenoid goiter"
 - Autoimmune disease
 - Gland structure is replaced by dense lymphocytic infiltration
 - A short period of thyrotoxicosis followed by hypothyroidism
 - Other autoimmune disease:- as Addison's, Rh, arthritis, pernicious anemia
 - c) **Subacute** viral thyroiditis " de Quervain disease"
 - d) Riedel's thyroiditis: Fibrous tissue infiltration of thyroid "woody thyroid"
 - e) Iatrogenic: thyroidectomy, radio-iodine, antithyroid drugs

B. Secondary: Simmond's disease (Pituitary myxoedema)

Clinical picture: common in female 30-50 years

1- General:

1. Intolerance to cold
2. Tiredness, weakness & weight gain
3. Face
 - Expressionless, bloated
 - Puffy eye lids & loss of outer 1/3 of eyebrows
 - Malar flush and thick skin
 - Red glazed tongue
 - May be cataract

2- Thyroid gland: according to cause

1. Enlarged: in Hashimoto's disease, endemic goiter & goitrogenous substance
2. Atrophic: in primary idiopathic forms
3. Scars of previous operation
4. Hard & fibrotic in Riedel's thyroiditis

3- Genital:

1. Females:

- Menorrhagia
- Galactorrhea, sterility (hyperprolactinemia due to feed back ↑TRH)

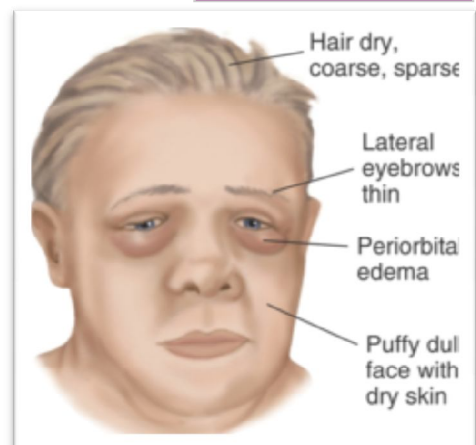
2. Males: impotence, gynecomastia.

4- GIT:

1. Tongue : red glazed
2. Stomach: dyspepsia, hypochlorhydria (leading to Fe deficiency anemia)
3. Intestine low motility → **constipation** & slow absorption → steatorrhea

C/P:- 6G + eye + CNS

General
Gland
Gonadal
GIT
جلدSkin
CVS
Neurological
Blood



5- Skin

- **Dry**, cold, non sweaty, pale (anaemia - oedema) may be scaly and rough
- **Non pitting edema**: due to SC mucinous
- **Nails** are thick - body **hair** is sparse & brittle.
- **Yellowish**:- due to carotinemia (lack of conversion of carotene to Vit A)

6- CNS:

1. Slow **celebration**, apathy, poor memory – Rarely myxoedema madness
2. Speech: slurred speech (mucinous material in tongue) with hoarseness of voice
3. Nerve deafness
4. Peripheral neuritis, carpal tunnel syndrome
5. Suspended jerks: delayed relaxation of tendon jerks
6. Others: ataxia, vertigo, convulsions
7. Myxoedema coma
 - Precipitated by cold, narcotics, anesthesia, infections
 - **Hypothermia** leads to muscle rigidity with both metabolic & resp. **acidosis** and multisystem depression (brain, heart, kidneys, liver) = **Heart failure**
 - **Hypoglycaemia** + **High mortality** is at least 50%

7- CVS:

1. **Hypertension** due to ++peripheral resistance & atherosclerosis (hypercholesterolemia)
2. Angina & intermittent claudication especially on start of treatment
3. Cardiomyopathy
4. Pericardial effusion (cholesterol pericarditis)
5. ECG: low voltage, sinus bradycardia, flat or inverted T (reversible)

8- Blood: 3 forms of anemia

- Normocytic normochromic (BM inhibition)
- Microcytic (Fe deficiency): ↓absorption + ↑loss due to menorrhagia
- Macrocytic anemia: associated pernicious anemia

Investigations:

1. TSH level: high in thyroid failure & low in pituitary failure (test of choice).
2. T4 & T3, PBI, FTI, radio iodine uptake are low.
3. T3 resin uptake, prolactin, cholesterol, CPK, GOT & GPT levels are high.
4. Glucose tolerance: flat curve
5. Thyroid antibodies
6. Blood: 3 forms of anemia- see before
7. ECG: see before

Differential Diagnosis:

1. Thyroid from pituitary myxoedema
2. Nephrotic syndrome
3. CRF
4. Pernicious anemia
5. Myotonic syndrome

Treatment:**A- Cretinism:**

- Treatment should start before first 6 months to prevent mental retardation.
- L – Thyroxin 0.025 mg / day to be increased up to 0.2 mg / day.

B- Adult hypothyroidism:

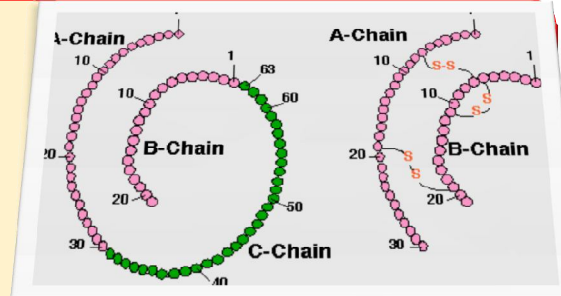
- L– Thyroxin for life: start by 50 ug/day & ++ gradually up to 100 – 200 ug/day.
- Old people & those with IHDs need lower dose (to avoid HF & angina)
- Follow up: ECG: cholesterol level, **TSH level (most important)**

C- Myxoedema coma:

- Gradual warming
- O2, ventilation & CVS support
- Glucose IV for hypoglycemia
- Drugs:
 1. T3 -2.5-5-Lgm/8h. or by nasogastric tube
 2. Hydrocortisone
 3. Antibiotics for infection

Introduction to Diabetes Mellitus

Insulin:- peptide hormone secreted from the B-cells of pancreas formed of 2 peptide chains bound together with di sulphide bound.
secreted as pro-insulin(Insulin+ C-peptide) the C-peptide split out to let the active form.



Action: Mainly **Metabolic action**

▪ **Carbohydrate:** **Glucose lowering effect.**

- Increase glucose uptake:- in skeletal muscles and adipose tissue (glucose transporter (GLUT 4). In liver (by increasing the activity of glucokinase enzyme). No role on brain, lens, intestinal mucosa, RBCs, and kidney.
- Increase glycogenesis (+ gly. synthetase) and inhibits glycogenolysis (hepatic phosphorylase).
- Inhibits gluconeogenesis.

▪ **Fat:** **anabolic**

- Increase lipogenesis (excess glucose is converted into FFA).
- Inhibits lipolysis: inhibits hormone sensitive lipase enzyme in adipose tissue.

▪ **Protein:** **anabolic**- Inhibits proteolysis and gluconeogenesis

▪ **Electrolytes:** **intracellular shift of K**

factors affecting Insulin (regulations)

Stimulatory	Inhibitory
- Glucose - AAS (Arginine, glycine) - Glucagon like peptide - Gastrin - Secretin - CCK	- Cortisol - Catecholamines - GH - Thyroxine - Estrogen-progesterone

Diabetes Mellitus

Definition:-

It is a metabolic disorder of carbohydrate metabolism due to relative or absolute insulin deficiency leading to hyperglycemia, glucosuria.

With secondary disturbance of lipid (lipolysis and ketosis) and protein metabolism (catabolic = negative N2 balance).

Usually complicated with micro and macro-angiopathy

Aetiology:

- Primary (95%)
- Secondary (5%)
- Gestational DM

I- Primary DM: include 3 types:

- Type I
- Type II
- MODY

	Type I DM Juvenile-Insulin dependent DM	Type II DM Maturity onset-Non insulin dependent DM
Incidence	5-15%	85%
Prevalence	0.3%	3-5%
Age of onset	<40 years	>40 years
Genetic locus	Chromosome 6-recessive	Chromosome-11 multifactorial
Body weight	Thin	Obese 80%-non obese 20%
Insulin level	Insulinopenia	Early increase-Late decrease
Ketoacidosis	Ketolabile	
Treatment	Insulin	Diet - Oral drugs - Insulin
Types	Type IA: Transient antibodies (80%) Type IB: Persistent antibodies (20%)	♦ Obese (mainly central) 80%: may lead to insulin resistance by adipocyte secretion of leptin, resistin. ♦ Non-Obese 20%
Pathogenesis	♦ In genetically predisposed patients (HLA- DR3 & DR4), infection by certain viruses (Coxsackie B4, mumps or retroviruses) antibody against islet cells. <u>Evidences of genetic predis.</u> ♦ 30% in identical twins ♦ Negative family history:- 2.5-5% in Child of diabetic father 1.25-5% in Child of diabetic mother	Possibilities: ♦ Insulin exhaustion ♦ Decreased insulin receptors number or responsiveness. ♦ Dyshormonogenesis ♦ Increased glucagon <u>Evidences of genetic predis</u> ♦ 100% in identical twins . ♦ highly positive family history:- 25% of patients have 1st degree relative with type-II DM.
pathology	♦ The islet cells are infiltrated by lymphocytes. ♦ the destruction of islet cells	♦ The islet cells show deposition of amyloid material (amylin) which is co-secreted with insulin.

Mature onset diabetes in the young (MODY):

- Intermediate between type I & type II
- Autosomal dominant
- Occurs in young obese patients
- Treated by oral antidiabetic drugs
- Associated by chlorpropamide alcohol flush phenomenon due to release of VD material as Pgs or encephalins.

II- Secondary DM:**1. Pancreatic causes:**

- Chronic pancreatitis
- Pancreatectomy
- Cancer body
- Fibrocalculus pancreatopathy (Chronic malnutrition)
- Cystic fibrosis
- Hemochromatosis

2. Endocrinal causes:

- Pheochromocytoma
- Cushing
- Thyrotoxicosis
- Conn's syndrome
- Acromegaly
- Gucagonoma
- Somatostatinoma

3. Others:

- Drugs: thiazides, cortisol, diazoxide, C. Pills.
- Receptor defect:
 - Down's Klinefelter and Turner's syndromes
 - Friedreich's ataxia, myotonia congenita, Huntington's chorea
 - DIDMOAD (DI, DM, Optic Atrophy & Deafness) syndrome
- Liver cirrhosis

III- Gestational DM:-

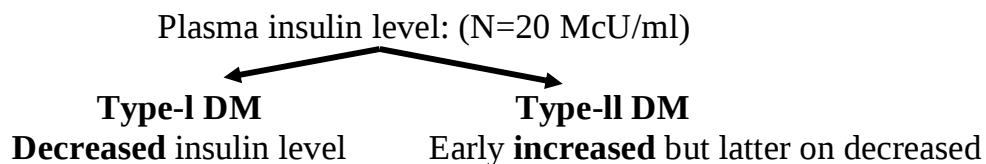
- It develops in 3% of pregnancies especially in 3rd trimester.
- The insulin reserve is not sufficient in pregnancy.
- Glucose level return to normal few weeks after labor.
- 30-50% develop DM after 10-15 years.

Diagnosis of gestational DM:

1. Fasting blood sugar > 126 mg% or
2. Oral glucose tolerance test:-
 - ♦ Patient is screened at 25th week of pregnancy with 50 gm oral glucose
 - ♦ Suggested by blood glucose $\geq$ 140-150 mg% one hour after glucose ingestion
 - ♦ Oral glucose tolerance test: after 100 mg oral glucose:
 - Fasting $\geq$ 105 mg%
 - 1st hour $\geq$ 190 mg%
 - 2nd hour $\geq$ 165 mg%
 - 3rd hour $\geq$ 145 mg%

Clinical picture:

1. Asymptomatic in 1/3 of cases and accidentally diagnosed by blood sugar test.
2. **Polyurea**: osmotic diuresis due to hyperglycemia (nocturnal enuresis in children)
3. **Polyphagia** with loss of body weight: defect in the satiety center or in Leptin.
4. **Polydipsia**
5. **Pain and paresthesia** secondary to peripheral neuritis.
6. **Premature loosening of teeth**.
7. **Blurred vision**: due to osmotic swelling of lens.
8. Symptoms of complication.

Investigations:**Hormonal level:****Hormonal effect:-****1. Blood sugar test:**

	Normal	Diabetic
Fasting	80-120 mg%	>126 mg% (7.0 mmol/l)
2hrs PP	<140 mg%	>200 mg% (11.1 mmol/l)

mmol/l X 18 = mg%

2. Glucose tolerance test:-

- Patient should be fasting (overnight).
- Fasting blood sugar is done
- Bladder is emptied
- The patient is fed 75 gm glucose orally, and blood sugar level and urine testing for glucose is performed every 1/2 hr for 2 hrs.
- Diagnosis of diabetes is done according to the above mentioned criteria.

3. Corticosteroid-glucose tolerance test: Dexamethzone 3 mg is given before GTT, Patients with latent DM give a diabetic curve

4. Urine analysis:

- Glucosuria: occurs when glucose serum level exceeds 160 mg%, but it is not a good indicator for DM diagnosis or assessment of treatment?
- Ketonuria: for diagnosis of diabetic Ketoacidosis.

Causes of glucosuria:

1. Renal glucosuria: hereditary low renal threshold
2. Lag storage curve (alimentary glycosuria): late dumping syndrome & thyrotoxicosis
3. Stress hyperglycemia
4. Reducing substances in urine e.g. salicylates & Vit C

5. Home blood glucose monitoring

3- Others

C- peptide: reflecting endogenous level (islet cells activity)

Investigations of the **cause** in secondary DM:- e.g. Hormones level, LFTs

Investigations for **complications**:- e.g. blood ketone level, KFTs, ECG

Investigation to assess treatment efficacy:

Glycosylated hemoglobin (Hb A 1c):- Non enzymatic glycosylation of hemoglobin.

- Hb A 1 c is synthesized over the life of RBCs in proportion to the degree of glycemia.
 - Gives an index of the blood glucose over the life of Hb molecule (2-3 months).
 - Normally it is less than 6% - if > 12% → Poor glycemic control in the past 3 months.
- Glycosylated Albumin but has more rapid turnover than Hb.*

Criteria for diagnosis of DM:

1. Classic symptoms of DM + Random plasma sugar ≥ 200 mg/dl
2. Fasting plasma glucose ≥ 126 mg/dl + post prandial glucose ≥ 200 mg/dl
3. Random plasma glucose ≥ 200 mg/dl

**>2
occasions**

Stages of DM :

Pre diabetes : (impaired glucose tolerance=IGT) =

IGT:- between the normal and diagnostic values of DM (FBS:- 110-126 mg%)

Potential DM:- normal GTT with increased risk of DM

- Positive family history.
- Obesity.
- Renal glucosuria
- Female with history of overweight baby.

Latent diabetes:- Diabetes appears only on exposure to stress (e.g pregnancy)

Chemical diabetes:- Raised blood glucose with no symptoms.

Clinical diabetes (Overt):- symptoms of DM + hyperglycemia which may be complicated or non-complicated.

Management of DM

1. **Diet Control:**

a. Indication:-

1. Mild cases of type-II DM
2. Adjuvant treatment in other cases

b. Diet regulation:

Caloric requirements = ideal weight x activity:

- Mild activity: 25-30 Cal/Kg / d (about 1600-1800 cal/d)
- Moderate activity : 30-35 Cal/kg/d (about 2400 cal/d)
- Over activity & pregnancy : 60 Cal/kg/d (about 3000 cal/d)

Food components:-

CHO: 50%

- Avoid simple sugars (mono saccharides) - Polysaccharides are absorbed slower with lower blood glucose peak.
- Avoid alcohol: high calories + potentiates hypoglycemia of insulin & sulphonyl urea + potentiates lactic acidosis of biguanides
- Artificial Sweeteners could be used: aspartame (carcinogenic?)

Fats: 30% : Avoid saturated fats

Proteins: 20%

Vitamins: Supply Vitamins: B complex & Vit A

Fibers (non-absorbable polysaccharides e.g. bran) to delay glucose absorption and form bulk to decrease appetite.

Number of meals:

3 main meals + 2 snacks in between to avoid hyperglycemic peaks or hypoglycemia with treatment.

2. Reduction of **body weight** should be the target in obese patients.

Pharmacological treatment

I- Oral Anti-diabetic Drugs:-

1. **Sulfonyl Urea:**

2. **Biguanides**

3. **New drugs**

	<u>1- Sulfonyl Urea</u> See table below	<u>2- Biguanides</u> Metformin (<i>glucophage</i>): 500 mg t.d.s. after meal
Action	1- Stimulate release of insulin from pancreases 2- Sensitize insulin receptors 3- Reduce glucose release by liver	1- Stimulate anaerobic glycolysis 2- Sensitize insulin receptors 3- Decrease glucose absorption from the gut 4- Decrease appetite
Indication	1- Type II-DM not controlled by diet alone 2- MODY type	1- Used alone in obese type II DM after diet failure 2- Combined with sulphonyl urea or insulin (obese)
Contraindication	1- Type I DM & history of DKA 2- During pregnancy 3- Type II DM during stress : e.g. trauma, operations, severe infection	<u>Any acidotic condition</u> 1- Renal impairment 2- Lung impairment
Side effects	1- Allergy (skin rash) 2- Hypoglycemia 3- Cholestatic jaundice 4- Weight gain 5- Chlorpropamide: alcohol intolerance 6- Aplastic anemia 7- Cardiomyopathy	1- GIT irritation 2- Metallic taste of mouth 3- Anti vitamin B12 absorption 4- Lactacidosis

Sulfonyl Urea drugs:

Pharmacological name	T. name	Duration of action (H)	Daily Base
First generation			
▪ Tolbutamide	Rastinon	6-12	0.5-2 gm
▪ Acetohexamide	Dimelor	8-24	0.25-1.5 gm
▪ Chlorpropamide (renal)	Pamidine	24-72	0.1-0.5 gm
Second generation			
▪ Glipizide	Minidiab	6-12	2.5-30 mg
▪ Glicazide (liver)	Diamicon	10-12	40-320 mg
▪ Glibenclamide (renal)	Daonil	10-20	2.5-15 mg
▪ Glimepride	Amaryl	7-12	1-8 mg

3- New Drugs:➤ **Glucosidase inhibitors: Acarbose** (glucobay)

Action:- Inhibits glucosidase enzyme on the brush border of intestine, thus inhibiting **carbohydrate absorption**.

Side effects: flatulence & diarrhea – rarely liver dysfunction

Dose:- 50 mg TDS

➤ **Pioglitazone:** insulin **sensitizer** & inhibits **gluconeogenesis**➤ **Repaglinide (Novonorm):** stimulate insulin production at meal time.

Dose: 0.50-1 mg before meals.

➤ **Dipeptidyl Peptidase-4 Inhibitors (DPP4):-** Galvus - Januvia - Onglyza**II- Insulin:****Indications:**

1. Type I DM.
2. Type II DM in special circumstances.
 - Uncontrolled by diet or oral drugs.
 - Pregnancy
 - Stress: infections, trauma, operations

N.B. Other uses of insulin:

- Treatment of **hyperkalemia**
- Test of **growth hormone** level
- Insulin tolerance test in **panhypopituitarism**

**Sources of insulin:-**

- Bovine insulin :- obsolete (not used now)

Human insulin by genetic engineering	Insulin analog synthetic-made insulin like
2- Regular insulin	1- Rapid-acting (Aspart - Glulisine - Lyspro)
3- Intermediate acting insulin	4- Long-acting (Levemir - Lantus)

1- Rapid-acting insulin:- begins after 15 minutes, peaks in 1 hr and last for 2-4 hrs.

Types: Insulin glulisine (**Apidra**) - insulin lispro (**Humalog**) - insulin aspart (**NovoLog**)

2- Regular or Short-acting insulin:- begins within 30 minutes, peaks from 2-3 hrs and last for 3-6 hrs.

Types: Humulin R, Novolin R

3- Intermediate-acting insulin:- begins within 2-4 hrs, peaks in 4 -12 hrs and is effective for 12-18 hours.

Types: NPH (Humulin N, Novolin N)

4- Long-acting insulin tends to lower glucose levels over a 24-hour period.

Types: Insulin detemir (Levemir) and insulin glargine (Lantus)

5- Biphasic (mixture) formed of Short + long

Types :- Rapitard, Mixtard, initard

➤ Oral insulin and Intra nasal insulin under trials

Dose of insulin:

A. Conventional method:

1. Start with 10 units regular insulin before every meal and monitor blood sugar before and after meals to adjust insulin dose accordingly. Calculate the total daily dose. Alternatively start by 10-20 U/day in normal weight individuals, and 25-30 U/day in obese ones.
2. Give mixed insulin (mixtard) once in the morning. Poorly controlled patients should be placed on twice daily insulin injections with 2/3 of the total dose before breakfast and 1/3 before supper.
3. Modify the dose as follows
 - Day time hyperglycemia is an indication to increase morning dose
 - Bed time & breakfast hyperglycemia is an indication to increase evening dose

B. Multiple subcutaneous insulin injection

- Administration of 25% of the daily dose as intermediate insulin before sleeping
- 75% of the dose is given as regular insulin 30 min before meals (3 doses)

C. Infusion devices (pumps): continuous subcutaneous insulin infusion (CSII)

- Small pump is strapped around the waist
- Insulin is delivered at a basal rate continuously throughout the day via a needle in the subcutaneous tissue of the abdominal wall.
- The patient can deliver meal time doses by touching a button on the machine

Administration:

- Insulin is given SC in different places of skin
- Insulin pump
- Insulin pens

Complications:

1. **Hypoglycemia** & hypoglycemic coma
2. **Smoggy** effect: nocturnal hypoglycemia (resulting in night sweats, night mares, lassitude and morning headache) which causes rebound morning hyperglycemia – treatment is by **reducing** night doses.



3. **Eleven** O'clock hyperglycemia: due to high level of cortisol – treatment by increasing dose of neutral insulin before breakfast + mid day light snack.
4. **Blurring** of vision: osmotic changes of lens.
5. Acute **neuropathy**: may occur paradoxically with controlling hyperglycemia by insulin.
6. Insulin **oedema**: mild LL edema (salt & water retention)
7. **Weight** gain
8. Insulin **lipodystrophy**:
 - Insulin lipoatrophy: Autoimmune reaction to non- human insulin
 - Insulin lipohypertrophy: lipogenic effect of insulin
9. **Allergy**: use human insulin
10. Insulin **resistance**: defined as daily requirements > 200 IU due to:
 - Obesity: commonest cause for mild resistance
 - Antibodies against insulin receptors: as in acanthosis nigricans

N.B. New Trends in Treatment Of DM:

1. *Pancreatic transplantation*
2. *Pancreatic islet cell transplantation: given intra-peritoneal to replicate in liver*
3. *Pancreatic pump (closed loop system)*

TREATMENT OF TYPE I DM

1. Diet control as mentioned
2. Insulin therapy as mentioned
3. Interventions in prediabetic stage(+ve antibodies):
 - ♦ Neonatal and early infancy deprivation of cow milk
 - ♦ Immunosuppression by cyclosporine or azathioprin ??
 - ♦ Antioxidants

TREATMENT OF TYPE II DM

1. Diet as mentioned but with targeting weight reduction in obese patients
2. Oral hypoglycemic in patients not controlled by diet alone
3. Insulin:-
 - ♦ Used in **1ry failure** (no control by oral drugs) or **2ry failure** (initial response to oral therapy followed by failure)
 - ♦ Because of insulin resistance, higher doses than type I may be required
4. Prevention of type II:- Indicated in patients with strong family history of DM or those with impaired glucose tolerance.
 - Metformin, ramipril and parvastatin may be helpful in delaying DM.
 - Diet control and exercise

Complications of DM

Pathogenesis of diabetic complications

CHO:-

Glucosuria if it exceeds renal threshold → polyurea with washing of H₂O soluble materials e.g. vitamins.

Glucose toxicity:- Hyperglycemia leads to

A- impairs the function of β-cells and the action of insulin on the peripheral tissue → **further rise in glucose level.**

B- Sorbitol theory:-

- Activation of **polyol pathway**: glucose reduction to **sorbitol** by aldose reductase → sorbitol exerts osmotic effect → cell injury in nerves, lens, kidneys, & BVs.

C- Glycosylation of

- Proteins and collagen: this will affect Hb, plasma proteins, BVs wall, lipids (become more **atherogenic**).

- Collagen of capillaries → narrowing of their lumens with increased permeability.

Lipolysis:- Release of fatty acids from adipose tissue → deposition in the liver → **fatty liver.**

Formation of **ketone bodies** (as a source of energy) which is toxic

Protein catabolic effect:- as amino acids converted to glucose (**-ve nitrogen balance**) & muscle **wasting.**

Other mechanisms: ↓ RBCs deformability, platelets aggregation, ↓ fibrinolysis and hyperlipidemia.

Top Ten

- I- Neurological
- II- Ocular
- III- CVS
- IV- Respiratory
- V- GIT
- VI- Urinary
- VII- Genital
- VIII- Cutaneous
- IX- Foot
- X- Brittle DM

I- Neurological Complications

A. Cerebral Complications

A. Cerebral Complications

- I. Hypoglycemia
- II. Diabetic Ketoacidosis "DKA"
- III. Hyperglycemic Hyperosmolar Non Ketotic
- IV. Diabetic Lactacidosis
- V. Cerebral Atherosclerosis
- VI. Diabetic Nephropathy

B. Spinal Cord Complications

C. Diabetic Neuropathy

I- Hypoglycemia - Hypoglycemic coma

Causes:

1. Commonest: missed meal after insulin or oral anti-diabetics
2. Others: brittle "early" DM
3. Severe exercise- poor drug elimination renal or liver failure.
4. Factitious
5. Unrecognized other endocrine disorders e.g. Addison disease.
6. Gastroparesis

Clinical picture: (CNS - Premonitory - Nocturnal)

I- Neuroglycopenic symptoms:

1. Rapid fall of glucose lead to convulsions then coma
2. Gradual fall of glucose will lead to headache, confusion and end in coma

II- **Premonitory** (adrenergic) symptoms are: tachycardia, palpitation, tremors, anxiety, sweating, pallor and fatigue.

III- Nocturnal hypoglycemia: night mares, morning lack of concentration, hallucination, parasthesia.

IV- Hypoglycemia may be asymptomatic.

1. Biochemical hypoglycemia:- 45 mg% blood glucose
2. Masked symptoms of hypoglycemia:- β - blockers, tranquilizers, during night, old, alcohol intake
3. Prolonged hypoglycemia leads to irreversible brain damage.

Diagnosis: low glucose in blood < 45mg% absent from urine.

Treatment:

1. Concentrated glucose 50% - 50 cc IV – followed by 10% infusion
2. IV or IM glucagon 1 mg
3. Oral glucose in early cases
4. Treatment of cause (close observation is needed in patients with long acting insulin or oral hypoglycemic drugs and need close observation.

DD of Hypoglycemia:

Definition: Glucose thresholds for hypoglycemia induced symptoms vary widely; accordingly the diagnosis depends on presence of **Whipple triad**:

- ♦ Symptoms of hypoglycemia
- ♦ Low blood glucose level
- ♦ Improvement of symptoms by glucose

a) Endocrinal causes:

1. *Hyperinsulinism due to :*

- ♦ Reactive hypoglycemia (Alimentary hypoglycemia): following gastrectomy (dumping syndrome) rapid glucose absorption leads to excessive insulin release
- ♦ Therapeutic: over treated DM either by insulin or sulphonylurea
- ♦ Early diabetics: Excessive release of insulin after a carbohydrate diet
- ♦ Insulinoma
- ♦ Paramalignant:- produce Insulin like growth factor-I (IGF-1)

2. *Decreased Anti-insulins: Addison's disease, Simmond's disease, myxedema.*

b) Non-endocrinal causes:

1. Deficient CHO intake: starvation & malnutrition, ethanol, anorexia nervosa, obstructive gut lesions.
2. Defect in absorption:
 - After gastrectomy, gastrojejunostomy (late dumping syndrome)
 - Malabsorption syndrome
3. Defective storage: liver cirrhosis, glycogen storage diseases.
4. Increased glucose breakdown: exercise, pregnancy, malignancy
5. Increase renal glucose loss: renal glycosuria, de Toni-Fancom syndrome.
6. Idiopathic post prandial hypoglycemia.

N.B. Post prandial hypoglycemia:-

Reactive hypoglycemia - Early diabetes - ethanol induced

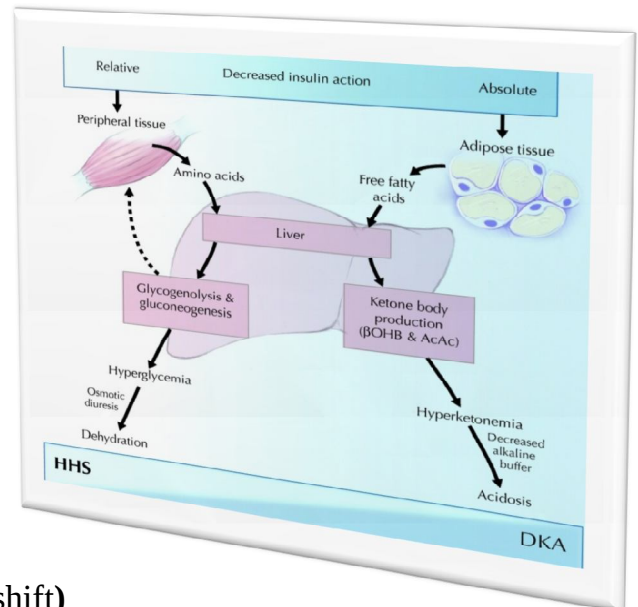
While other causes are fasting hypoglycemia.

I- Diabetic Ketoacidosis "DKA"

Definition:- Potentially life-threatening complication of DM characterized by **triad** of Hyperglycemia - Acidosis - Ketosis

Causes:

1. Neglected treatment.
2. Severe exertion, stress, steroid therapy, infection.
3. Tissue damage: trauma, operation, burns, shock, stroke, myocardial infarction
4. Pregnancy, labor & lactation.



Pathogenesis & clinical picture:

(4=hyperglycaemia-dehydration -acidosis -K shift)

1. Glucose can't enter muscles & fat cells in absence of insulin leading to **hyperglycemia & glucosuria**
2. Glucosuria lead to severe polyurea, polydysia & **dehydration** with dry inelastic skin, sunken eyes, thirst, low BP & low temperature.
3. Fat is mobilized for energy production leading to excess production of **ketone bodies** (acetoacetic & α - hydroxybuteric acids) with ketosis, ketonemia & ketonuria.

Effects of ketosis:

- a. **Muscles:** generalized weakness & muscle pain due to absence of energy
 - b. **Kidney:** ketonuria, together with glucosuria
 - c. GIT: acute abdomen = epigastric pain, nausea, vomiting, constipation, hematemesis (ketone bodies in stomach mucosa).
 - d. Respiration: deep rapid **Kussmaul breathing** = air hunger" with acetone breath
 - e. CVS: depressed contractility, with peripheral VD
4. **Shift of K outside cells** (in absence of insulin) which is then list in urine
 5. **End stage:** collapse & coma due to acidosis, ketosis, dehydration & electrolyte imbalance

Investigations:

1. Blood:

- a. Hyperglycemia, ketonemia
- b. Acidosis (-- plasma HCO_3), dehydration (++PCV) -++ FFA & TG
- c. Electrolyte: ++ K (extracellular shift) & ++ Na (Dehydration)

2. Urine: glucosuria (4 +) , ketonuria, polyurea

Complications:

1. Cerebral oedema due to rapid reduction of blood glucose
2. ARDS
3. Thrombo-embolism
4. Serious infections e.g. mucormycosis
5. DIC
6. Acute circulatory failure

Treatment: (4=hyperglycaemia-acidosis-dehydration-K shift)

1. Hospitalization & care of comatosed

2. **Fluid replacement:**

- Saline (0.9%) 1 L over 30 min → 0.5 L/30 min → 0.5 L/1 hr → 0.5 L/2 hrs till HR & BP return normal.
- Once blood sugar drops below 200 mg%:- Replace by 5% glucose (1L /4-6 h) to avoid hypoglycemia.

(Average fluid deficit 6 L (3L extracellular + 3L intracellular)

- If plasma Na > 155 mg% → give saline 0.45% till Na falls to 140 mg%

3. **Regular insulin** "low dose regimen":

- **0.1 U/kg/hr continuous infusion** (6 units/hr) or deep IM .
- Follow up by blood sugar every hour & give further insulin according to it.

4. **Treatment of acidosis:** in severe case (PH < 7.1, HCO₃ < 12 mEq) we give 1/2 - 1 L of 1/6 molar NaHCO₃ IV.5. **Correct plasma K level.**

Hyperkalemia is present at first due to extracellular shift.

Hypokalemia occurs with insulin ttt due to intracellular shift:

If K < 3.5 mg% : add 20 ml KCl (40 mEq) to each 1L of fluid given

If K 3.5-5. Mg%: add 10ml KCl (20 mEq) to each 1 L of fluid given

If K > 5.5 mg%: give no K

6. Others:

- Correct cause & precipitating factors.
- Prophylactic antibiotics
- Nasogastric tube: to aspirate gastric content in cases with severe vomiting.
- Heparin IV in old & dehydrated patients to guard against DIC.
- O₂ if pO₂ < 80 mmHg.

Summary

Effect		C/P	ttt
Insulin deficiency	1- hyperglycemia	Polyurea - polydipsia	Regular Insulin (initial then continuous infusion)
	2- Dehydration	Dehydration	Fluid replacement (Saline then glucose 5%)
Lipolysis = Ketosis	3- Acidosis	Kaussmaul b. Acidosis	Correction of acidosis In severe cases :- NaHCO ₃ IV
K shift	4 - K shift out		K-CL 40 mEq to each 1L

	Hypoglycemic coma	DKA
Onset	Acute	Gradual
Pulse	Rapid with good volume	Weak and rapid
BP	High	Low (dehydration + acidosis)
Respiration	Normal	Rapid
Temperature	Normal	Subnormal or fever (infection)
Breath	Normal	Acetone
Pupil	Dilated	Normal
Tongue	Normal	Dry
Skin	Sweaty	Dry
Coma	Irritable	Non-irritable
Urine	No glucose	Glucose + acetone
IV glucose	Rapid recovery	No effect

II- Hyperglycemic – Hyperosmolar Non – Ketotic Coma HHNK

Causes: it occurs in old type II DM due to

1. Absence of fat reserve or fat mobilization (relative lack of GH or cortisol)
2. Insensitive thirsty center lead to dehydration aggravated by use of diuretics
3. Precipitating factors: infection, infarction.

Clinical picture:

1. Severe hyperglycemia : often > 900 mg% + severe dehydration (with marked ++ PCV, ++Na)
2. No ketosis
3. Pre-renal uremia may occur due to dehydration
4. Neurologic symptoms: convulsions, hemiparesis. Stupor & coma occur when serum osmolality is > 340 mosm/L (normal 290 mosm/L)

Treatment: as DKA

1. Fluids: 1/2 normal saline 1L/hour not faster to avoid cerebral edema.
2. Insulin: smaller amount than ketoacidosis
3. Heparin : since there is ++ incidence of DIC

III-Diabetic Lactacidosis

Cause :

1. Diabetic patients taking biguanides.
2. Precipitating factors: pneumonia, myocardial infarction (ischaemia).

Clinical picture: of acidosis i.e. Kussmaul respiration – late CNS, CVS inhibition.

Treatment: NaHCO₃ + insulin – glucose combination

DKA	HHNK	Lactic acidosis
- Hyperglycemia - Acidosis (pH < 7.3) - H_2CO_3 < 15 meq/L. - Positive ketones.	- Hyperglycemia (> 600mg/dL). - high serum osmolality No acidosis (pH > 7.3) - No ketones	- Severe acidosis pH < 7.3 H_2CO_3 < 15 meq/L. - No ketones. - Serum lactate > 5 mmol/L

IV-Cerebral Atherosclerosis: Common in diabetics – may end in coma

V- Diabetic Nephropathy: May end in CRF & coma

B. Spinal Cord Complications

1. Amyotrophic lateral sclerosis
2. Anterior spinal artery occlusion

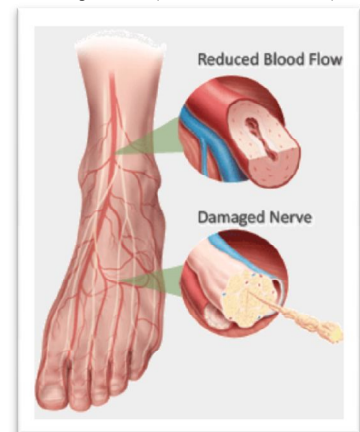
C. Diabetic Neuropathy

Pathogenesis:

1. **Microangiopathy:** due to ischemia of vasa nervosa
2. **Macroangiopathy:** 2ry to atherosclerosis
3. **Hypovitaminosis:** Polyurea wash water soluble B complex vitamins
4. **Metabolic ketosis:** toxic effect of ketones bodies
5. Transformation of glucose to **sorbitol** by aldose reductase enzyme (*polyol pathway*)

Clinical picture:

1. Features of PN may precede the discovery of DM.
2. Starts as Mononeuropathy or mononeuritis multiplex
 - a. P.N.: sciatic, femoral, ulnar, median
 - b. Cranial N. : optic neuritis, 3,4,6 palsy, facial palsy, Argyl-Robertson pupil
3. Polyneuropathy:
 - a. Mainly sensory: early tender calf, paresthesia, later on stock & glove hyposthesia occur.
 - b. Early loss of deep sensations: vibration sense, lost muscle sense "pseudo-tabes"
 - c. Motor weakness is late and rare.
4. Autonomic neuropathy: characteristic
 - a) **CVS:**
 - Postural hypotension (orthostatic syncope)
 - Tachycardia & fixed H.R. –Silent myocardial infarction
 - b) **Chest:** respiratory arrest (unknown cause)
 - c) **Genito-urinary:**
 - Impotence (neurogenic –vasogenic – psychogenic)
 - Bladder (sensory, motor, autonomic bladder)
 - d) **GIT:**
 - Delayed gastric emptying, with indigestion (gastroparesis diabeticorum)
 - Early nocturnal diarrhea, stagnant. Loop syndrome, late constipation



- e) **Skin:** hyper-hydrosis or anhydrosis –VD (with edema) or VC
- f) **Trophic changes:** ulcers, rough mail, loss of hair, tapering of finger, charcot's neuropathic joint.

Treatment:

1. Strict control of DM: diet, oral hypoglycemic, better insulin
2. Physiotherapy for muscle weakness
3. Drugs:
 - a) Vasodilators: nicotinic acid, nifedipine
 - b) Anti-platelets: aspirin, diopyridamol
 - c) Capillary modulators: Ca dobesilate (Doxium)
 - d) Vitamins : B 1, B6, B12-ATP (adenoplex)
 - e) Analgesics: aspirin, Carbamazepine (Tegretol)
 - f) Aldose reductase inhibitor:- Sorbinil

II- Ocular complications

1. **Lid:** blepharitis, sty, xanthelasma (from hypercholesterolemia)
2. **Conjunctiva:** conjunctivitis
3. **Pupil :** Argyl Robertson pupil – Homer's syndrome
4. **Ocular muscles:** external ophthalmoplegia (3,4,6 palsy)
5. **Lris:** Rubeosis iridis (vascularization ending in glaucoma)
6. **Lens:** errors of refraction – diabetic cataract
7. **Retina :** "diabetic retinopathy"

Pathogenesis:

- DM causes increased thickness of capillary basement membrane with increased permeability.
- Aneurismal dilatation may occur in some vessels while others become occluded
- Chronic retinal hypoxia may lead to neovascularization and increased vascular permeability. (Especially in type I DM of long duration).

- It is of 2 types:

- a. **Proliferative:** neo-vasculatures: this will lead to hemorrhage and retinal detachment.
- b. **Non-proliferative:** microaneurysm, hemorrhages, exudates (benign form)

8. **Macula:** maeulopathy, macular edema which may end in loss of vision

9. **Optic nerve:** retrobulbar neuritis ending in optic atrophy.

Treatment of diabetic retinopathy:

1. Strict diabetic control with insulin
2. Photocoagulation by laser to destroy new vessels
3. Viteroretinal surgery:- Remove vitreous hemorrhage – repair detached retina
4. Calcium dobesilate "doxium" regulates capillary permeability & neovascularisation.

III- Respiratory Complications

1. Pulmonary infection especially TB (TB follows DM as its shadow)
2. Dyspnea, air hunger (Kussmaul respiration), acetone odour during ketosis

IV- Cardio-Cardiovascular Complication

Pathological changes and presentation

1. **Microangiopathy:** retinal, renal, vasa nervosa
2. **Macroangiopathy:** due to atherosclerosis
 - a. **Cerebral :** thrombosis, ischemia
 - b. **Coronary:** angina, Mlm arrhythmia. Recently coronary microangiopathy is described.
 - c. **Peripheral:** intermittent claudication , gangrene
 - d. **Renal:** renovascular hypertension, due to renal artery atherosclerosis
3. **Cardiac:** cardiomyopathy, probably due microangiopathy.
4. **Blood pressure:**
 - a. Hypertension
 - b. Hypotension: postural (autonomic neuropathy)

Treatment:

1. Treatment of hypertension:
 - Avoid thiazides : they are hyperglycemic
 - Avoid non selective B-Blocker : mask warning symptoms of hyperglycemia
 - Best drugs : ACEI, Angiotensin II blockers, Ca channel blockers.
2. Treatment of hyperlipidemia : low fat in diet, polyunsaturated oils, hypocholesterolemic drugs
3. Stop cigarettes: ↑ risk of microangiopathy & coronary heart disease

V- GIT Complications

1. **Mouth :** inflamed gums, dental caries, loose teeth , red glazed tongue
2. **Stomach:**
 - Dyspepsia due to hypochlorhydria, and autonomic neuropathy
 - In ketosis: pain, nausea, vomiting, hematemesis
3. **Intestine :** autonomic neuropathy leads to nocturnal diarrhea & stagnant loop syndrome
4. **Liver :**
 - Fatty infiltration
 - Tender during ketosis due to glycogen depletion
5. **Gall bladder:** chronic non-calicular cholecystitis due to hyperlipidemia and hypomotility.

VI- Urinary Complications

1. **Infections:** cystitis, pyelonephritis esp necrotizing pyelitis
2. **Neurogenic bladder:** sensory atonic bladder
3. **Stones:** from stasis & recurrent infection
4. **Diabetic nephropathy**

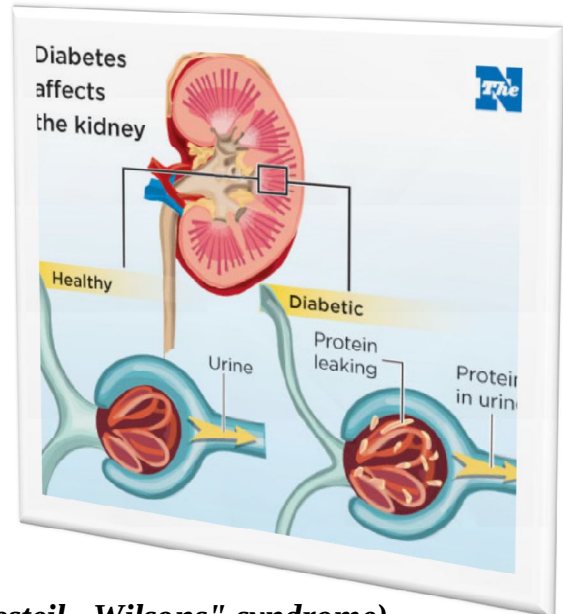
Diabetic Nephropathy

I- Glomerular Injury

Diabetic glomerulosclerosis

Aetiology:- Long standing DM (type I, type II) especially poor controlled. Onset within 10-20 years. High correlation occur with diabetic retinopathy & diabetic neuropathy

Pathology:- 2 types: Nodular glomerulosclerosis & Diffuse glomerulosclerosis



A. *Nodular glomerulosclerosis: ("Kimmelsteil – Wilsons" syndrome)*

1. 25% of case
2. Thickening of BM due to muco-polysaccharide nodules deposition in between & inside glomeruli
3. Microaneurysms of small blood vessels, hyalinization of afferent arterioles.

B. *Diffuse glomerulosclerosis:*

1. 75% of case
2. Diffuse thickening of BM (in absence of nodules) + interstitial atrophy.
3. Hyalinization of afferent & efferent arterioles with atherosclerotic changes

Clinical picture:

1. **Onset:** asymptomatic **proteinuria** " micro-albuminuria" .Later on frank proteinuria occur, which may extend to the classic **nephrotic** syndrome.
2. Renovascular **hypertension**
3. Years later the picture of **CRF** supervenes

Clinical stages:-

A- Incipient nephropathy

Stage1	Nephromegaly	Hyperfiltration (high GFR)
Stage 2	As stage1 +	Exertional microalbuminuria (20-200 ug / min)
Stage 3	As stage 2 +	Constant microalbuminuria

B- Overt nephropathy

Stage 4	proteinuria > 0.5 gm / 24 hour + pass into nephrotic syndrome + low GRF & hypertension .
Stage 5	end stage renal disease "ESRD"

Investigations:

1. Of DM:
2. Urinary: earliest is **microalbuminuria** by radioimmunoassay of urine (dipstick is less accurate). Late: frank **proteinuria** with hyaline & granular casts.
3. Renal function test: late rise in urea, creatinine.

Treatment:

1. **Strict control of DM:** we may use multiple SC insulin injection, but with ↓ in insulin dose (insulin being metabolized in kidney).
2. **Strict control of hypertension:** Best is ACE inhibitors as "captopril, enalapril" or angiotensin II receptor blockers as Losartan.
3. **Treatment of RF:**
 - a. Symptomatic control
 - b. End stage: chronic ambulatory peritoneal dialysis is better than hemodialysis
 - c. Recently: simultaneous renal & pancreatic transplant.

II- Interstitial Injury**"Diabetic interstitial nephropathy"****A. Ischemic injury ; interstitial injury leads to :**

- Diminished GRF
- Renovascular hypertension
- RTA (hyporeninemic hypoadosteronism) with hyperkalemia, hyperchloremic acidosis & hypertension.

B. Acute pyelonephritis**C. Acute necrotizing papillitis****VII- Genital Complications****1. Males :**

- Impotence together with lost deep testicular pain, due to autonomic neuropathy
- Intact testicular sensation indicates psychogenic impotence

2. Females :

- Menorrhagia
- Pruritus vulvae
- Sterility

3. Diabetes with pregnancy:**• Effects of pregnancy on DM**

- a. ↑ Needs for insulin due to anti-insulin: estrogen, progesterone, lactogenic H.
- b. ↓ Renal threshold for glucose (lost in urine)
- c. ↑ Incidence of complications e.g. nephropathy.

• Effects of DM on pregnancy:

Maternal	Baby
1. Abortion	1. High birth weight " macrosomia "
2. Premature labor	2. Hypoglycemic baby (overactive pancreas)
3. Pre-eclampsia	3. Congenital anomalies esp. anencephaly.
4. Post partum hemorrhage	4. Hyaline membrane disease (↓ surfactant) RDS
5. Puerperal sepsis	5. ↑ Incidence of neonatal death

Management of DM during Pregnancy:

1. Monitor DM by blood glucose not urine (renal threshold falls in pregnancy)
2. Insulin ttt with frequent administration –
3. Avoid oral hypoglycemic since they cause fetal B cell hypertrophy and hence tendency of macrosomia. In addition they are teratogenic.
4. Keep fasting blood glucose at 110 mg% & 2h PP below 150mg
5. Avoid weight gain
6. Hospitalization at 36-38 weeks
7. Discontinue insulin after labor & shift to oral drugs
8. Repeated glucose administration to the baby

Management of DM during Surgery:

1. Stop oral drugs or moderate & long acting insulin 2 days before surgery and should be replaced by short acting insulin.
2. Glucose- insulin + potassium solution should be infused during surgery
3. Post operatively maintain infusion till patient is able to eat

VIII- Cutaneous Complications

- Infections: carbuncle, furuncle , abscesses, cellulitis, fungal infections.
- Delayed healing of wound
- Pruritus: Pruritus vulvae
- Necrobiosis lipoidica diabetorum:- Painful violaceous plaque with central tellowish area surrounded by brownish border, usually on shin of leg (cutaneous B1,vessels occlusion) Central ulcaeration, healing by scar.
- Diabetic dermopathy "spotted leg syndrome" :-Painless reddish papules usually over shins of tibia, may heal leaving scar & pigmentation.
- Bullosis diabetorum: superficial bullae, with clear serum which may be hemorrhagic
- Granuloma annulare: papules arranged in ring, with depressed center, over extensor surface of fingers.
- Xanthomata & xanthelasma: hyperlipidemia
- Caroteneinemia: defect conversion of carotene to vitamin A in liver + excess vegetable intake.
- Complications of insulin ttt: lipoatrophy & lipohypertrophy

CarotenemiaBullosis diabetorumGranuloma annulareNecrobiosis lipoidica diabetorum

IX- Foot Complications

1- Ischemia:

- a. **Acute:** pain, pallor and cyanosis ending in gangrene
- b. **Chronic:** ↓ skin temp, loss of hair, trophic ulcers, loss of distal pulse.

2- Neuropathy:

- a. Trophic ulcers: over pressure points
- b. Neuropathic joint: Charcot's joint (painless, deformed & hyper mobile)

3- Infections: fungal & bacterial infections are due to:

- a. Suppressed immunity
- b. Microangiopathy with ischemia
- c. Hyperglycemia in tissue



Treatment:

1. Control of diabetes
2. Foot care & hygiene: Repeated wash, drying, powdering, cutting toenail straight to avoid in growing toenails.
3. For infection: antibiotics, drainage of pus, excision of infected tissue & bone.
4. For ischemia: revascularization or amputation in gangrene.

X- Brittle DM

Definition: Unpredictable fluctuations of blood glucose with recurrent attack of hyperglycemia and/or hypoglycemia.

Aetiology:

A- Causes of recurrent hypoglycemia:

1. Over treatment by insulin
2. Renal failure
3. Low renal threshold
4. Other hidden endocrinal problems e.g. pituitary or adrenal insufficiency.
5. Gastroparesis: may lead to difficulty in matching the time of food absorption to that of insulin peak.
6. Uncooperative patient.

B- Causes of recurrent hyperglycemia:

1. Inter-current illness e.g. infection.
2. Inappropriate insulin dose

Treatment:

1. Revision of treatment schedule
2. Insulin pump
3. Patient education

Pancreatic Endocrinal Tumors

Endocrine tumors of the pancreas arise from the APUD (Amine precursor uptake and decarboxylation) cells. They may occur with other endocrine tumors as a part of MEN.

Gastrinoma (Zollinger-Ellison syndrome)

Tumors arise within the "gastrinoma triangle" formed by porta hepatis, neck of the pancreas and the third portion of the duodenum.

The tumor secretes large amount of gastrin that stimulates acid secretion.

Clinical picture:

1. Peptic ulcer: tend to be large, difficult to treat and recur rapidly.
2. Malabsorption and diarrhea:- high HCL inactivates pancreatic juice

Investigations:

1. Endoscopy:- huge or multiple PUs $\pm$ watermelon stomach
2. High HCL
3. Secretin test: IV secretin (2u/Kg) produces rise in serum gastrin > 200 pg/ml
4. High fasting serum gastrin level (> 150 pg/ml)
5. CT, MRI, Indium-labeled octreotide scintigraphy, angiography and portal venous sampling of gastrin to localize the tumor.

Treatment:

1. Surgical removal of the tumor
2. Metastatic tumors are treated by Omeprazole or chemotherapy.

Glucagonomas:- arise from β -cells and secrete glucagon. C/P:- DM and abdominal rash

Somatostatinoma:- arise from D-cells. C/P:- DM, steatorrhea, and weight loss.

Vipomas:- tumor secreting vasoactive intestinal polypeptide (VIP). Causing severe watery diarrhea (pancreatic cholera). Treatment:- octreotide, or surgical resection.

Insulinoma

- The tumor is benign in 95% cases

Clinical Picture:

- The main presentation is fasting hypoglycemia
- May be psychiatric manifestation (bizarre behavior, amnesia & automatism).
- Focal neurological manifestations may occur.

Diagnosis: is based on fulfilling the **whipple triad**:

- Symptoms of **hypoglycemia** with fasting or exercise
- Low blood **glucose** level when symptoms are present
- Symptoms are relieved by glucose **administration**

Investigations:

1. FBS and insulin:- (3 occasions) hypoglycemia with high insulin level (> 5 mU/L)
2. High proinsulin serum level
3. High level of c-peptide
4. CT, MRI, Indium-labeled octreotide scintigraphy, angiography and portal venous sampling to localize the tumor site.

Treatment:

- Surgical removal of the tumor
- For inoperable tumors : diazoxide or octreotide may suppress insulin secretion.

Hirsutism

Definition:- unusual hair growth in abnormal places of female body (beard, mustache, chest, axilla, abdominal midline, pubic area and thigh).

Represents a state of hyperandrogenism from the ovary or the adrenals.

Aetiology:-

1. Familial
2. Racial
3. Idiopathic
4. Polycystic ovarian syndrome
5. Ovarian androgenic tumors
6. Congenital adrenal hyperplasia
7. Cushing
8. Adrenal tumors
9. Obesity:
10. Drugs: androgen, diazoxide and cyclosporine.

Gynecomastia

Definition: Hyperplasia glandular tissue of the male breast (increase fatty tissue of the breast is called lipomastia)

Aetiology:

I- Physiological:

1. Neonatal
2. Puberty
3. Old age

II- Pathological:

1. Liver disease
2. Estrogen producing tumors (testis & adrenals)
3. Acromegaly
4. Carcinoma of the breast
5. Hyperthyroidism
6. Drugs:

Non-hormonal:- Spironolacton - Digitalis - cannabis - Cimitidine - cytotoxic

Hormonal:- Anti-androgen - Estrogen (in cancer prostate) - Gonadotrophins

Obesity

Definition: increase in body fat content with increased BMI > 30 in males and > 28 in females.

Aetiology:

1. Simple obesity: Several factors have been linked to several factors:

- Genetic factor: A new gene (ob gene) in chromosome 7 has been found to be responsible for the production of new protein (Leptin) that causes suppression of feeding center in the hypothalamus.
- Decreased energy expenditure: if associated with over feeding.
- Excessive energy intake: high caloric diet (high fat and carbohydrate).
- Familial or racial: sharing the same pattern of life or genetically.

- Decreased B2-adrenergic (as catecholamine induced lipolysis).

2. Endocrinal causes:

- Frolich's and Laurant Moon Biele syndromes
- Hypothyroidism
- Cushing syndrome
- Pregnancy
- Hypogonadism

3. Hypothalamic disturbances: as tumors or inflammation. It presents by polyphagia, polydipsia, polyurea and hypersomnia.

4. Drugs: corticosteroids, contraceptive pills, phenothiazines and antiepileptics.

Diagnosis:

1. Comparison of individual weight with charts for ideal body weight to height.

2. Calculation of body mass index (BMI) = $\frac{\text{Weight (KG)}}{\text{Height (m}^2\text{)}}$

- 20-25 Kg/m² (Acceptable)
- 25-30 Kg/m² (Over weight)
- > 30 Kg/m² (Obese)
- > 40 Kg/m² (Morbidly obese)

3. Measurement of skin fold thickness over the middle of the triceps muscle (Normally in Male < 20 mm and in females < 30 mm)

4. Regional fat distribution can assessed by: **(type of obesity)**

• Calculating: $\frac{\text{Waist circumference}}{\text{Hip circumference}}$

	Central (visceral obesity)	Peripheral (gluteo-femoral)
W/H ratio	> 1 in men > 0.9 in women	< 0.85 in men < 0.75 in women
CVS diseases	high incidence	



- CT or MRI of the abdomen to provide accurate estimation of the visceral fat.

Complications:

1. Cardiovascular:

- Hypertension is partly related to insulin resistance and hyperinsulinemia
- Atherosclerosis due to increased levels of LDL and decreased level of HDL
- Ischemic heart disease
- Arrhythmia and sudden death
- Varicose veins

2. Neurological:

- Pseudotumor cerebri
- Stroke

- Depression
- 3. Pulmonary:
 - Obstructive sleep apnea
 - Obesity hypoventilation syndrome
- 4. Gastro-intestinal:
 - Fatty liver
 - Gall bladder stones and cholecystitis
 - Hiatus hernia
- 5. Endocrinal:
 - Non-insulin dependent diabetes mellitus
 - Earlier menarche and menopause and irregular cycles
 - Growth hormone is reduced
- 6. Musculo-skeletal:
 - Osteoarthritis
 - Gout due to impaired urate clearance
- 7. Cutanouse:
 - Increased skin friability with increased risk of fungal and yeast infection
 - Acanthosis nigricans
 - Delayed healing of wounds
- 8. Cancer: increased incidence of :
 - Endometrial and postmenopausal cancer breast
 - Cancer prostate in men

Metabolic Syndrome X:

- Impaired glucose tolerance
- Hyperinsulinemia usually associated by obesity
- Hypertension
- Hyperlipidemia

Treatment:-

1. Diet:
 - Reduction of caloric intake to 1000 Kcal/day
 - Diet should be made of 100 gm complex carbohydrates, 50 gm of proteins, and 40 gm of fat.
2. The aim is to lose one kilogram/week
3. Exercise: this not enough to lose body weight without dietary restriction
4. Appetite suppressing drugs: These drugs should be used as an adjuvant to diet control **Only in patients with BMI > 30 Kg/m²**
 - **Drugs enhance release of epinephrine:**
 - Mazindol 1-2 mg PO
 - Diethyl propion : 25 mg TDS
 - **Drugs block reuptake of epinephrine :** phenylpropanolamine 25 mg TDS
 - **Drugs block the release and reuptake of serotonin :** Fenfluramine: 25 mg TDS.
 - **Silbutramine (Meridia 10-15 mg/day):** It reduces food intake (through β_1 activation) & increases metabolic rate (through β_3 activation).
 - **Orlistat (Xenical):** 120 mg/8 hrs, it inhibits intestinal lipase



5. Surgical:

- Indication:
 - ♦ BMI > 40
 - ♦ BMI > 35 with family history of heart attack or diabetes.
- Methods:
 - ♦ Jejunum-ileal bypass: causes malabsorption
 - ♦ Gastric placcation: Creating a small gastric pouch.
 - ♦ Gastric balloon: By endoscopy.
 - ♦ Liposuction for regional obesity.

Value of reducing 10 Kg in a patient initially 100 Kg:

1. Reduction in mortality: 25%
2. Reduction in risk of DM: 50%
3. Fall in BP : 10 mmHg
4. Fall 10% in cholesterol, 15% LDL, 30% in TGs, and ↑HDL 8%.

Multiple Endocrine neoplasm "MEN"

{Polyendocrine Adenomatosis "PEA"}

I- Hyper-function:-**I- MEN I :Wermer syndrome (3Ps)**

- Hyperparathyroidism: ++Ca
- Pancreatic islet cell tumor: gastrinoma (Zollinger Ellison) or insulinoma
- Pituitary adenoma: ++GH, prolactin.
- Less common: adrenal & thyroid tumors ± : multiple cutaneous lipomas

II- MEN II A : (Sipple's disease)

- Adrenal tumors: pheochromocytoma
- Cushing
- Thyroid tumors: medullary thyroid carcinoma (++ calcitonin)
- Hyperparathyroidism

III- MEN II B : As Sipple + mucosal neuromas + skeletal abnormality**II- Hypo-function:****1. Schmidt disease**

- Hypoadrenalism : Addison's
- Hypothyroidism: Myxoedema

2. Multiple endocrine autoimmune candidiasis (MEDAC):

- Hypoadrenalism
- Hypoparathyroidism
- Candidiasis of skin & mucous membranes